Coupling reactions using flow-generated diazo compounds

A dissertation presented by

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Declaration

This dissertation is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy. Unless specifically indicated in the text, the research described is the result of my own work and not the product of collaboration.

Jian Siang Poh
July 2017

Statement of Length

This thesis does not exceed the word limit of 60,000 as set by the Degree Committee for the Faculty of Physics and Chemistry.

Jian Siang Poh
July 2017

Acknowledgements

I have met many wonderful people over the past few years, and I dedicate this section to the numerous individuals who have come and gone from both the Whiffen and ITC labs.

The first toast of course goes to Steve Ley – it seems so long ago arriving back in 2012, hopelessly naïve as a summer student looking to tinker around in the lab… You have been an excellent and supportive supervisor during my time here, I could not wish for anything more!

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I have split the following chronologically according to the dates that people left (roughly), so without further ado…

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flow machine! ☹ I know you spent so long trying to get it to work in the first place…), but it was delightful having you in the Tesco Bay and visiting your house to play 'drunk' Monopoly! Daniela de Lucia, it was great to have you in the bay next to us, always cheerful even though the chemistry and column purification sucked – really, thank you for being such a inspiring presence! Seriously, stop stealing the money from the Monopoly bank! My 'wingman' Rohan Merchant, it was so motivational to have you there with us on the late weekday evenings up to midnight and the Saturday stints, I think I would have been a LOT lazier over the past few years if I wasn't inspired by you. Thank you for all the philosophical discussions we had about chemistry and life walking back to West Cambridge from the department, and of course for looking after 'incapacitated' me immediately after the first Christmas Ley Group dinner! ☺

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Abstract

In recent years, the exploitation of flow technologies as an enabling tool to access unique chemical reactivity has flourished. This dissertation describes the utilisation of these flow methods to access new sets of highly versatile, unstable diazo compounds and their application in coupling reactions.

In the first chapter, an introduction into the structure and reactivity of diazo compounds is provided, as well as a discussion of currently available methods for their generation.

The second chapter describes the coupling of flow-generated, semi-stabilised diazo compounds with terminal alkynes for the synthesis of racemic di- and trisubstituted allenes, using copper(I) catalysis.

The third chapter follows with an account of creating chiral disubstituted allenes by asymmetric coupling of flow-generated, semi-stabilised aryl aldehyde-derived diazo compounds with terminal alkynes, using a copper(I) catalyst and a newly developed pyridine(bisimidazoline) ligand.

The fourth chapter describes the generation of new, highly reactive non-stabilised diazo compounds and their reaction with arylboronic acids to allow metal-free ‘protodeboronative’ and ‘oxidative’ $C(sp^2)$-$C(sp^3)$ cross-couplings.

Finally, the fifth chapter describes the experimental procedures relevant for the results described in Chapters 2-4.

Abbreviations

Δ	heat
δ	chemical shift in parts per million
λ_{max}	wavelength at peak maximum
μ	micro
ν_{max}	frequency at peak maximum
[α]	specific rotation
°C	degrees Celsius
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
approx.	approximately
aq.	aqueous
Ar	aryl
atm	atmosphere
AU	absorbance unit(s)
B	base
BIM	bisimidazoline
BIPHEP	2,2'-bis(diphenylphosphino)biphenyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
BPR	back pressure regulator
br	broad (NMR spectroscopy and IR spectroscopy)
Bu	butyl
c	centi
c	concentration
ca.	*circa*
Cbz	carboxybenzyl
cm^{-1}	wavenumber
cod	1,5-cyclooctadiene

conv.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cyp	cyclopentyl
d	day(s) or doublet (NMR spectroscopy)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
dec.	decomposed
DEPT	distortionless enhacement by polarisation transfer
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
E	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv.	equivalent(s)
es	enantiospecificity
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia*
EWG	electron-withdrawing group

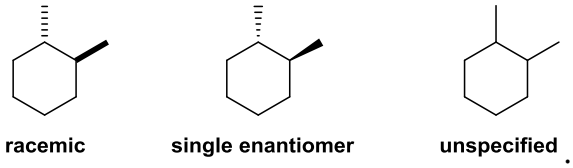
FEP	fluorinated ethylene propylene
FT	Fourier transform
g	gram(s)
h	hour(s)
Hex	hexyl
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i	iso
i.d.	inner diameter
IR	infrared
L	litre(s) or unspecified ligand
lit.	literature value
M	mega or unspecified metal
M	molar
m	medium (IR spectroscopy), metre(s), milli or multiplet (NMR spectroscopy)
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mmHg	millimetre(s) of mercury
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
m/z	mass-to-charge ratio
n	nano
n	normal

nbd	norbornadiene
n.d.	not determined
NMI	*N*-methylimidazole
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser spectroscopy
Nu	nucleophile
o	*ortho*
oct	octanoate or octet (NMR spectroscopy)
p	*para*
p-ABSA	4-acetamidobenzenesulfonyl azide
Pent	pentyl
Ph	phenyl
pin	pinacol
ppm	parts per million
Pr	propyl
PS	polymer-supported
Py	pyridine
q	quartet (NMR spectroscopy)
qn	quintet (NMR spectroscopy)
R	undefined substituent
rac	racemic
R_f	retention factor
r.t.	room temperature
s	singlet (NMR spectroscopy) or strong (IR spectroscopy)
SEGPHOS	bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
sept	septet (NMR spectroscopy)
S_N2'	bimolecular nucleophilic substitution with allylic rearrangement
sublim.	sublimed
T	temperature
t	triplet (NMR spectroscopy)
t	tertiary
TBAF	tetrabutylammonium fluoride

TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
TCP	tetra(4-chlorophenyl)porphyrin
terpy	2,2′:6′,2″-terpyridine
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
t_R	residence time or retention time
Ts	tosyl
UV	ultraviolet
W	watt(s)
w	weak (IR spectroscopy)
w.r.t.	with respect to
w/w	weight-to-weight ratio
X	undefined heteroatom
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Structure representation

This thesis uses the graphical representation of chemical structures based on the convention proposed by Maehr.* Solid and broken lines represent relative configuration and indicate compounds that are racemic, whereas solid and broken wedges are used to assign absolute configuration. Normal bond lines are used to describe stereocentres where the configuration is unspecified.



* H. Maehr, *J. Chem. Ed.* **1985**, *62*, 114-120.

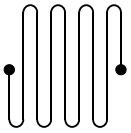
Flow technology diagrams

HPLC piston pump or peristaltic pump

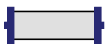
T-piece mixer

Unheated reactor coil

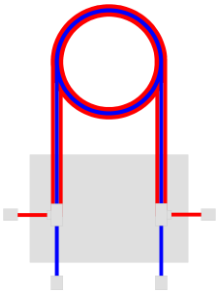
Heated reactor coil



Microfluidic reactor

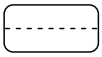


Omnifit® column reactor



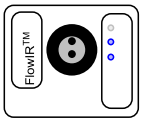
Tube-in-tube reactor

Vapourtec UV-150 photoreactor



In-line phase separator

Back-pressure regulator



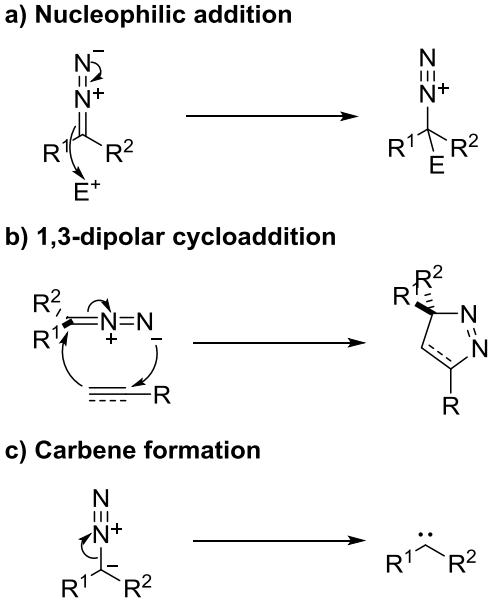
Mettler Toledo FlowIR® in-line IR spectrometer

Contents

1. Introduction to diazo compounds

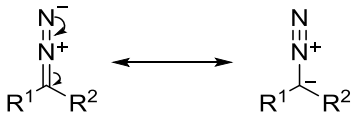
1.1. Properties and reactivity of diazo compounds

The simplest member of the diazo compound family, diazomethane, was first synthesised by von Pechmann in 1894.[1] Notorious for its acute toxicity and shock sensitivity, its properties are particularly illustrative of the dangers inherent to handling diazo compounds.[2] Indeed, the high reactivity and instability exhibited by many diazo compounds has meant that general preparative methods for these compounds remain limited in scope.[3] Despite these limitations, these species offer a myriad of unique reactivities, which are most conveniently split into three different types of processes: (a) nucleophilic addition; (b) 1,3-dipolar cycloaddition reactions; and (c) thermal or photolytic fragmentation to form singlet or triplet carbenes (Scheme 1).



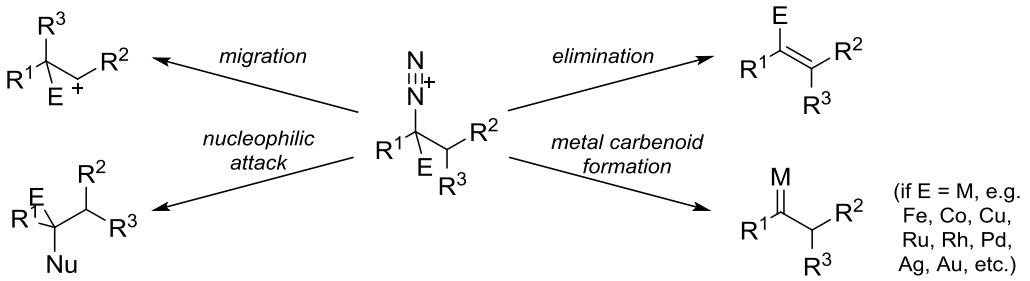
Scheme 1: Categories of typical reactivity pathways for diazo compounds.

Diazo compounds can be represented by two resonance structures, with a formal positive charge on the central nitrogen atom, and either a formal negative charge on the terminal carbon atom or on the terminal nitrogen atom (Scheme 2).



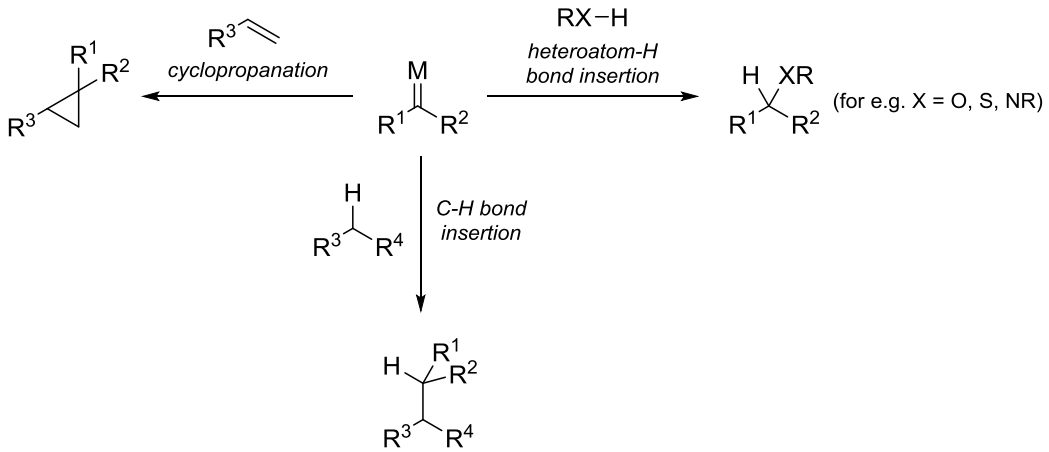
Scheme 2: Resonance structures of diazo compounds.

When considering the frontier molecular orbitals of diazomethane, the highest coefficient of the HOMO resides on the terminal carbon atom,[4] explaining the observed tendency of diazoalkanes to react *via* carbon with electrophiles, such as Brønsted/Lewis acids and metal salts. The transient alkyl diazonium species generated can then undergo a variety of transformations with concomitant extrusion of nitrogen gas, such as migration reactions, eliminations, nucleophilic additions, and in the case of reaction with metal salts, metal carbenoid formation (Scheme 3).[2]



Scheme 3: Reactivity pathways of the transient alkyl diazonium cation after nucleophilic addition of diazo compounds.

Whilst diazo compounds often act as nucleophiles *via* carbon, the corresponding metal carbenoid is electrophilic and can participate in complementary reactive pathways.[5,6] Further to this, metal carbenoids act as more controllable alternatives to highly reactive free carbenes. In the presence of the correct metal and ligand, it is possible to direct the reaction selectively towards, for example, cyclopropanation and C-H or heteroatom-H insertion reactions (Scheme 4).[7-9] Although free carbenes (often generated by the thermal or photolytic fragmentation of diazo compounds) are able to offer similar reactive pathways, the process is inherently less selective and often leads to a mixture of products.[10]



Scheme 4: Reactivity pathways of metal carbenoids formed from diazo compounds.

The ability of diazo compounds to act as nucleophiles is dependent on the electronic nature of two flanking groups either side of the diazo unit.[11,12] It is convenient to classify diazo compounds into three main classes: stabilised diazo compounds, semi-stabilised diazo compounds and non-stabilised diazo compounds (Figure 1).

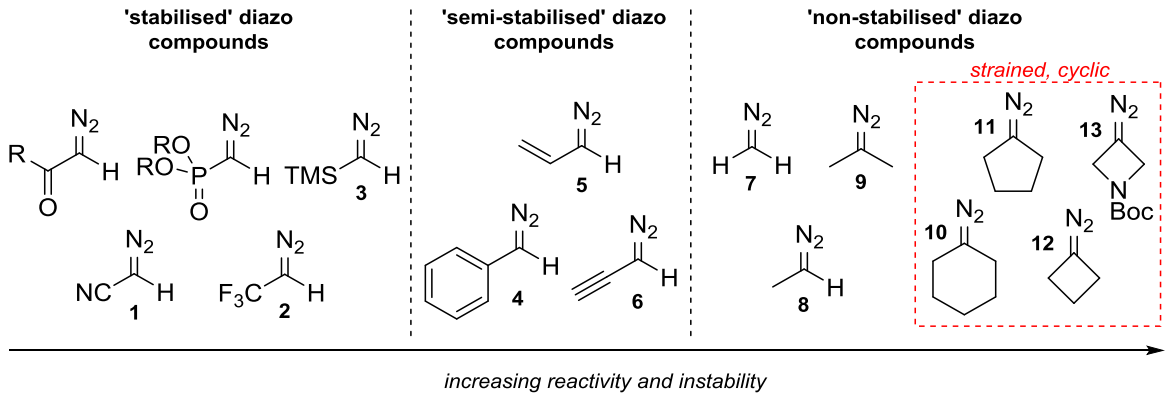
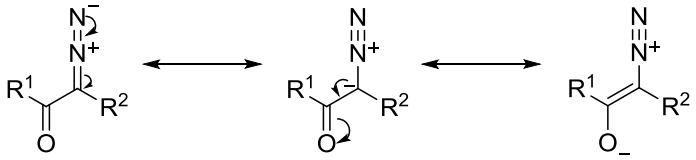


Figure 1: Classification of diazo compounds and their relative reactivities.

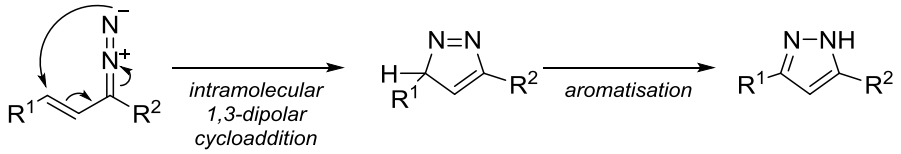
The most stable diazo compounds have an electron-withdrawing group on one or both sides of the diazo unit, either acting by π-conjugation (Scheme 5) and/or σ-withdrawal of electron density. Such stabilisation by carbonyl groups,[13,14] nitriles (e.g. **1**),[15] phosphonates,[16] CF_3 (e.g. **2**)[17,18] and silanes (e.g. **3**)[19] reduce the nucleophilicity of the diazo compound and are therefore less acid-labile. Indeed, many of these 'stabilised diazo compounds' are in fact stable to mild organic acids, such as acetic acid, and are also amenable to purification by silica gel column chromatography. Hence, the generation and use of these members of the diazo compound family is most widespread, especially for α-diazocarbonyl compounds.



Scheme 5: Mesomeric stabilisation in α-diazocarbonyl compounds.

Adjacent aromatic rings (e.g. **4**),[20] vinylic groups (e.g. **5**)[21] and acetylenic groups (e.g. **6**)[22] can also provide partial stabilisation of negative charge ('semi-stabilised diazo compounds'), though the effect is smaller compared to electron-withdrawing groups in the stabilised diazo compound family. Members of this family are more potent nucleophiles and are therefore more acid-labile, precluding their purification by silica gel column chromatography. The use of 'semi-stabilised diazo compounds' is more limited due to the difficulties in their

preparation and so most procedures generate the required diazo compound *in situ* from more stable precursors (Section 1.2). Vinylic diazo compounds present an additional complication as they are prone to cyclisation to pyrazoles (Scheme 6).[21]



Scheme 6: Cyclisation of vinylic diazo compounds to pyrazoles.

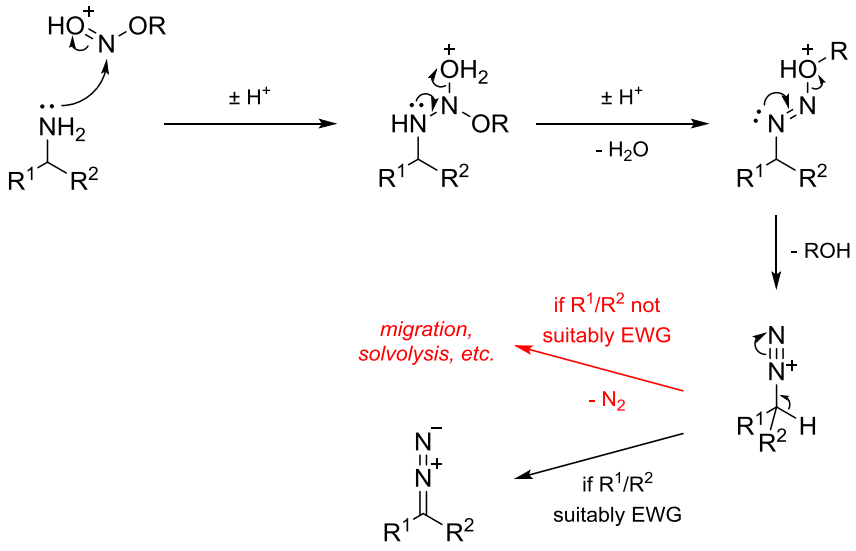
The final class of diazo compounds, 'non-stabilised diazo compounds', have either hydrogen atoms or alkyl groups on both sides of the diazo moiety (e.g. **7**-**9**).[12] When alkyl groups are present, the tendency to donate electron density through hyperconjugation further increases the negative charge on the carbon atom attached to the diazo group, increasing nucleophilicity, acid-lability and instability, thus making this family of compounds highly challenging to prepare and utilise. A further subdivision of this family involves *strained* non-stabilised diazo compounds (Chapter 4), containing a diazo group in a ring (e.g. **10**-**13**). These are among some of the most elusive reactive intermediates in organic synthesis, particularly for small ring sizes; the highly reactive and strained diazocyclobutane (**12**) has been prepared previously and decomposes at 0 °C,[23] whereas *N*-Boc-3-diazoazetidine (**13**) for example has never been observed – their intermediacy in some reactions are, however, implicated in various *in situ* protocols for aryl-alkyl cross-couplings.[24]

1.2. Synthesis of diazo compounds

Due to the wide variation in the stability of diazo compounds, numerous complementary methods have been developed to access stabilised, semi-stabilised and non-stabilised diazo compounds.[3,12] Two methods (diazotisation and fragmentation of nitrosoamide derivatives) can be classified as functional group manipulations from alkyl amine starting materials, whereas four more methods (base-mediated fragmentation of sulfonylhydrazones, oxidation of hydrazones, Forster reaction and photolysis of 1,3,4-oxadiazolines) can be classified as manipulations starting from aldehydes and ketones. The remaining method, the Regitz diazo transfer reaction, proceeds through deprotonation of carbonyl compounds followed by interception of the resulting enolate with an azide.

1.2.1. Diazotisation

A limited set of diazo compounds are accessible through the direct diazotisation of their corresponding amines.[3] When conducted under aqueous conditions, the amine is typically treated with sodium nitrite in the presence of acid (Scheme 7). The *in situ* generated nitrous acid allows nitrosylation of the amine, followed by elimination of water to form aliphatic diazonium ions. Diazotisation of water-sensitive derivatives can also be conducted in non-aqueous conditions by use of alkyl nitrite reagents and suitable organic Brønsted or Lewis acids (usually acetic acid or BF_3•Et_2O).[3] In the case where electron-withdrawing groups are attached (i.e. leading to the generation of stabilised diazo compounds), deprotonation at the α-carbon is facile and leads to formation of the desired diazo compound. However, the intermediacy of the aliphatic diazonium species is a major limitation to this method and is therefore not generally applicable to the generation of semi-stabilised or non-stabilised diazo compounds. Without the presence of stabilising electron-withdrawing groups, rearrangements and solvolysis resulting in thermodynamically favourable expulsion of nitrogen gas is a predominant reaction pathway.



Scheme 7: Mechanism of diazotisation of alkyl amines leading to formation of diazo compounds.

1.2.2. Base-mediated fragmentation of nitrosoamide derivatives

To circumvent the aliphatic diazonium intermediate problem posed by direct diazotisation of amines, it is possible to transform amines to nitrosoamide derivatives, through acylation/sulfonylation then subsequent nitrosylation. Various nitrosoamide derivatives

undergo cleavage in the presence of hydroxide ions, leading to the formation of diazo compounds. These derivatives are often based on carboxylic acid or sulfonic acid derivatives, including amides, carbamates, ureas, guanidines and sulfonamides (Figure 2).[3,12]

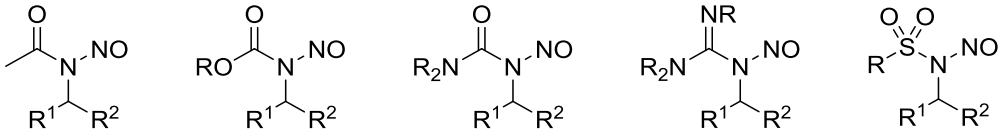
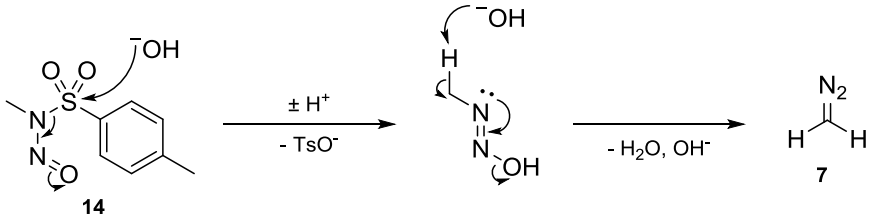


Figure 2: Commonly utilised nitrosoamide derivatives for the generation of diazo compounds.

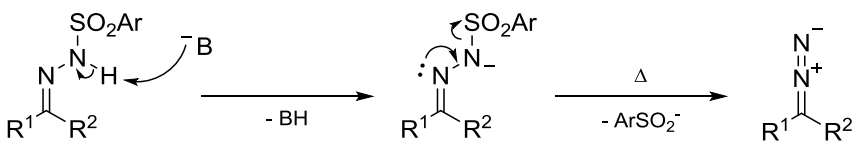
This method remains the preferred route to generating diazomethane (**7**), starting from the sulfonamide-based Diazald® (**14**) (Scheme 8).[25,26] The method can also be used for the generation of some of the other members of the non-stabilised diazo compound family, though yields after distillation become poorer with longer alkyl chain lengths due to their progressively higher boiling points.[21]



Scheme 8: Base-mediated fragmentation of Diazald® (**14**) to form diazomethane (**7**).[25,26]

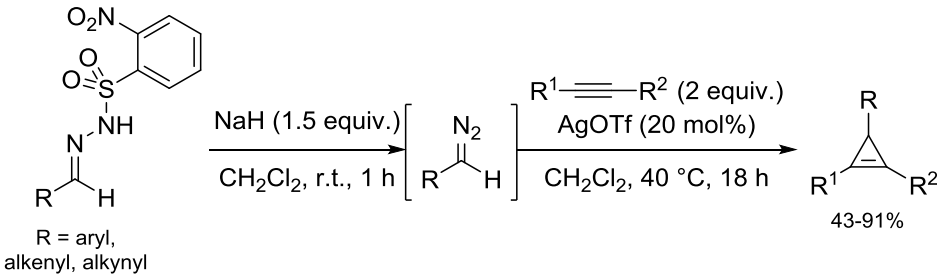
1.2.3. Base-mediated fragmentation of sulfonylhydrazones

Condensations of aldehydes or ketones with sulfonylhydrazides (usually *p*-toluenesulfonyl hydrazide, generating tosylhydrazones) generate the corresponding sulfonylhydrazones, which are potential precursors for the generation of diazo compounds *via* the Bamford-Stevens reaction. On heating (usually above 70 °C) in the presence of base, these sulfonylhydrazones can be deprotonated at nitrogen then eliminate sulfinate, thus generating the desired diazo compound (Scheme 9).[3,12]



Scheme 9: Base-mediated fragmentation of sulfonylhydrazones to form diazo compounds.

As diazo compounds are heat sensitive, particularly in the case of semi-stabilised and non-stabilised diazo compounds, procedures utilising this route typically proceed using *in situ* generation and interception with suitable substrates. Alternatively, electronically activated *o*-nosylhydrazones (Scheme 10),[27] have been demonstrated to be useful for the generation of aryldiazoalkanes at room temperature, which were then trapped with alkynes in a silver-catalysed cyclopropenation reaction.



Scheme 10: Generation and use of semi-stabilised diazoalkanes from *o*-nosylhydrazones as reported by Bi *et al.*[27]

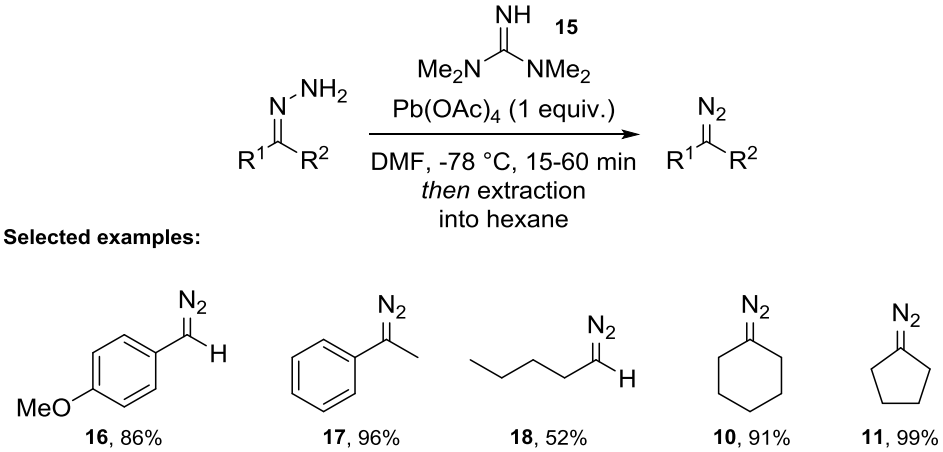
However, the generation of non-stabilised diazoalkane solutions remains elusive *via* this route and these are more commonly accessed through oxidation of hydrazones (Section 1.2.4).

1.2.4. Oxidation of hydrazones

A wide selection of metal-based oxidants are able to effect the dehydrogenation of hydrazones to diazo compounds, including HgO, $Pb(OAc)_4$, activated MnO_2, AgO and CuO. Of these, HgO and $Pb(OAc)_4$ and are the most widely used oxidants, able to provide access to highly sensitive non-stabilised diazo compounds, although undesirably, these oxidants are highly toxic.[3,12]

In the case of $Pb(OAc)_4$, initial investigations revealed that the production of acetic acid as a byproduct of the oxidation limited the reaction scope to stabilised diazo compounds.[28-30] The $Pb(OAc)_4$ method was developed further by Holton and Shechter.[31] Oxidations using this improved procedure were conducted at -78 °C in DMF using 1,1,3,3-tetramethylguanidine (**15**) as a basic additive, to prevent decomposition of semi-stabilised and non-stabilised diazo compounds by the acetic acid and to accelerate oxidation by forming the conjugate bases of the hydrazones, providing a wide variety of alkyl diazo compounds in good yields (e.g. **10**, **11**, **16-18**) (Scheme 11). Kingsbury *et al.* have subsequently disclosed that the

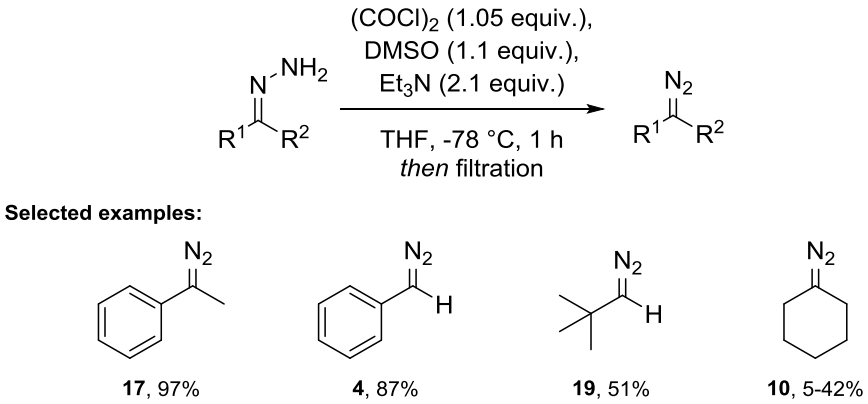
aforementioned $Pb(OAc)_4$/tetramethylguanidine oxidative system can be modified to be metal-free by replacing $Pb(OAc)_4$ with $PhI(O_2CCF_3)_2$, with no deleterious effect on the yield of the diazo compound.[32]



Scheme 11: Oxidation of hydrazones with $Pb(OAc)_4$ to generate semi-stabilised and non-stabilised diazo compounds as reported by Holton and Shechter.[31]

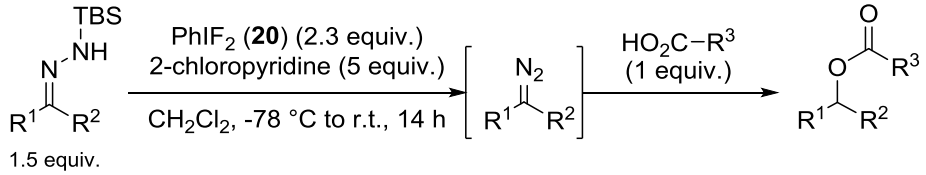
Oxidation of hydrazones with activated MnO_2 generally remains limited to the formation of semi-stabilised diazo compounds, i.e. for the oxidation of arylhydrazones and vinylhydrazones. Despite the lower toxicity profile compared to mercury- and lead-based oxidants, a major limitation associated with MnO_2 is the use of large excesses of the oxidant to provide synthetically useful conversions of the hydrazone to diazo compound.[3,12] The process is further hampered by excess oxidant causing decomposition of diazo compounds to their corresponding benzyl alcohols, aldehydes/ketones and azines.

Metal-free methods for the oxidation of hydrazones are also available. In 2007, Javed and Brewer described a highly useful modified Swern protocol for the generation of semi-stabilised aryldiazomethanes (e.g. **4**, **17**) in excellent yields (Scheme 12).[33] The generation of non-stabilised aliphatic diazo compounds is more challenging, with *tert*-butyldiazomethane (**19**) being produced in 51% yield and diazocyclohexane (**10**) being produced in capricious yields of 5% to 42%.



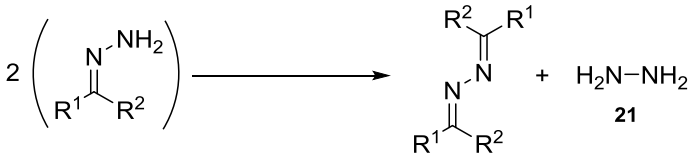
Scheme 12: Oxidation of hydrazones *via* a modified Swern protocol as reported by Javed and Brewer.[33]

A method described by Furrow and Myers in 2004 uses a hypervalent iodine reagent **20** to oxidise TBS-protected hydrazones to their corresponding diazo compounds, providing access to a variety of *in situ* generated semi-stabilised and non-stabilised diazoalkanes, which were subsequently intercepted with carboxylic acids for the formation of esters (Scheme 13).[34] However, the water-sensitivity and limited availability of the (difluoro)iodobenzene (**20**) oxidant is a significant limitation.



Scheme 13: *In situ* oxidation of TBS-protected hydrazones and trapping with carboxylic acids using $PhIF_2$ (**20**) as reported by Furrow and Myers.[34]

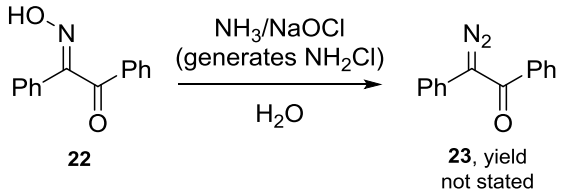
Overall, oxidative methods for the generation of diazo compounds offer some of the most versatile routes for the generation of all three families of diazo compounds. It should be noted, however, that the stability and synthesis of unprotected hydrazones *via* direct condensation of aldehydes or ketones with hydrazine is not always ideal, due to the possibility of the unprotected NH_2 group of the hydrazone reacting further with aldehydes or ketones to generate azines. Furthermore, unprotected hydrazones can undergo disproportionation to azines and hydrazine (**21**) (Scheme 14), which limits their utility as stable diazo compound precursors.[35]



Scheme 14: Disproportionation of unprotected hydrazones to azines and hydrazine (**21**).

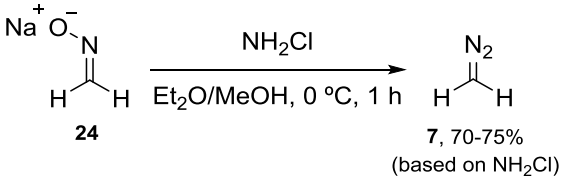
1.2.5. Forster reaction

Originally discovered in 1915 by Forster, the reaction of oximes (e.g. **22**) with chloramine allows the synthesis of a small selection of stabilised α-diazoketones (e.g. **23**) (Scheme 15).[36]



Scheme 15: Formation of stabilised diazo compounds *via* reaction with chloramine as reported by Forster.[36]

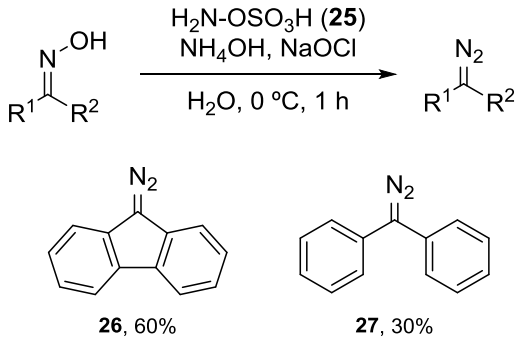
The Forster reaction is rarely used as a method of generating sensitive diazo compounds, however, due to the strong oxidising ability of chloramine, leading to incompatibility with a variety of functional groups. Using this method though, it is possible to generate solutions of diazomethane (**7**) from the sodium salt of formaldehyde oxime (**24**) (i.e. under basic conditions to limit acid-mediated decomposition) (Scheme 16);[37] it has not been hitherto possible to generalise this method for the synthesis of other non-stabilised aliphatic diazo compounds.



Scheme 16: Generation of diazomethane (**7**) from **24** *via* the Forster reaction as reported by Rundel.[37]

A related modification of the Forster reaction involves the use of hydroxylamine-*O*-sulfonic acid (**25**) as a substitute for chloramine. In the presence of aqueous base, some semi-stabilised diazo compounds (**26** and **27**) were generated in moderate yields (Scheme 17).[38] This modified method is also limited by the lack of generality, as attempts to generate the

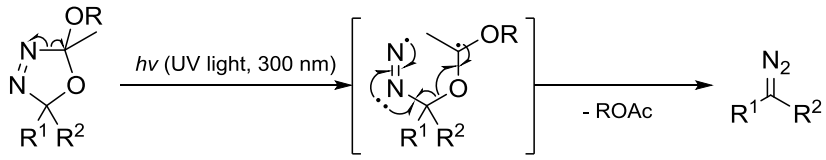
corresponding diazo compounds from acetophenone oxime and benzaldehyde oxime resulted only in low yields.



Scheme 17: Modified Forster reaction using hydroxylamine-*O*-sulfonic acid (**25**).[38]

1.2.6. Photolysis of oxadiazolines

The photolysis of 1,3,4-oxadiazolines represents an underutilised technique to generate diazo compounds, despite its general applicability to the synthesis of non-stabilised diazoalkanes. In 1989, Warkentin *et al*. described the fragmentation of 2-alkoxy-Δ^3-1,3,4-oxadiazolines under irradiation with 300 nm UV light, leading to the clean formation of diazo compounds – homolytic cleavage of the C-N bond leads to the formation of a diradical, which can subsequently fragment into a diazoalkane and an ester (Scheme 18).[39]

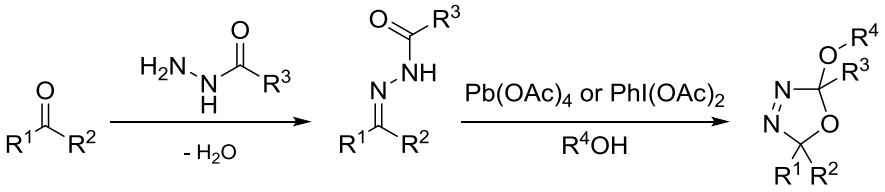


Scheme 18: Photolysis of oxadiazolines to form diazo compounds as reported by Warkentin *et al*.[39]

Although diazo compounds themselves are unstable to photolysis, their absorption maxima (*ca*. 220 nm and 440 nm) are significantly different to the photolytic wavelength required for the fragmentation of 1,3,4-oxadiazolines;[39] hence, utilisation of light sources that provide irradiation at solely *ca*. 300 nm represents a promising method to access non-stabilised diazo compounds using these precursors.

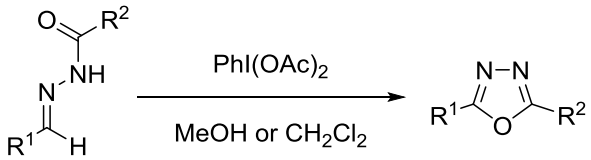
The 1,3,4-oxadiazoline diazo precursors are most conveniently accessed *via* the condensation of ketones with appropriate acylhydrazines to form the corresponding *N*-acylhydrazones.

Subsequent oxidation using either $Pb(OAc)_4$[40,41] or $PhI(OAc)_2$[42] in the appropriate alcoholic solvent allows the formation of the required precursors (Scheme 19).



Scheme 19: Generation of oxadiazolines *via* condensation then oxidative cyclisation.[40-42]

However, it should be noted that oxidation of an aldehyde-derived hydrazone does not form the required oxadiazoline precursor, since aromatisation to the more stable 1,3,4-oxadiazole occurs, representing a major limitation of this method (Scheme 20).[42]



Scheme 20: Formation of oxadiazoles from aldehyde-derived hydrazones after oxidation.

1.2.7. Regitz diazo transfer

The relatively acidic methylene unit in 1,3-dicarbonyl compounds, such as 1,3-diketones and β-ketoesters, can be deprotonated with a mild base and the resulting enolate intercepted with a variety of alkyl- and arylsulfonyl azides, including mesyl azide (**28**), triflyl azide (**29**), *p*-toluenesulfonyl azide (**30**) and *p*-acetamidobenzenesulfonyl azide (**31**) (Figure 3).[3,12]

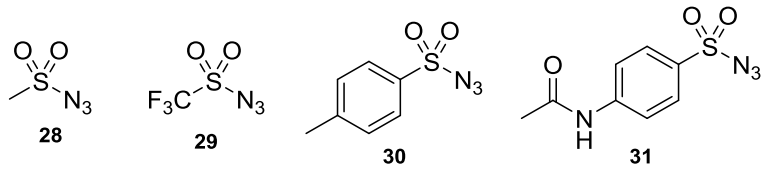
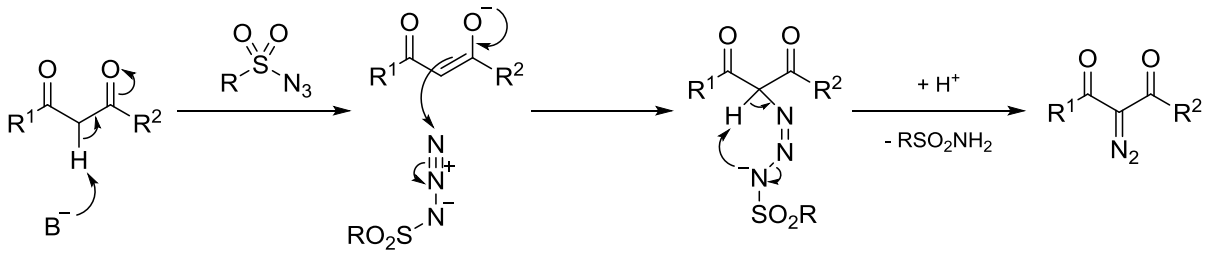


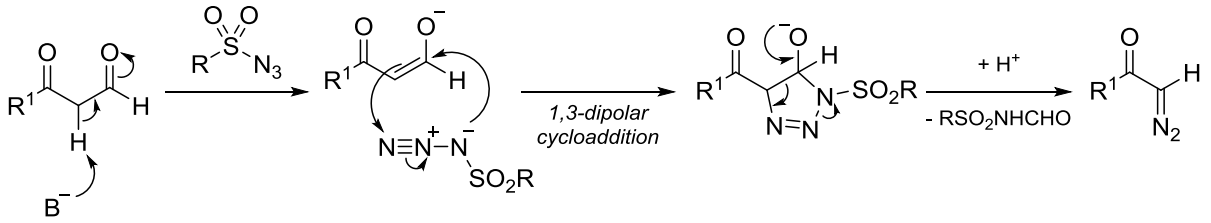
Figure 3: Commonly utilised azide reagents for the Regitz diazo transfer reaction.

This reaction, known as the Regitz diazo transfer reaction (Scheme 21), is a popular method to access stabilised α-diazocarbonyl compounds.



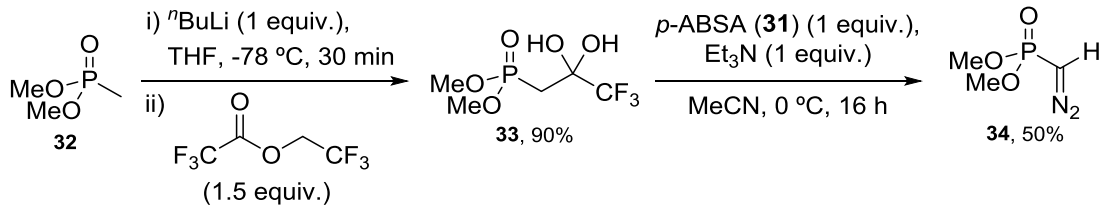
Scheme 21: Mechanism of Regitz diazo transfer.

In the case of less acidic methylene units in simple ketones and esters, the substrate can be activated towards deprotonation by means of introducing a formyl or trifluoroacetyl group (*via* Claisen reaction), then subjected to the diazo transfer reaction conditions. Deformylation or loss of the trifluoroacetyl group occurs in the process of diazo transfer, allowing the generation of various α-diazoketones and esters (Scheme 22).[3]



Scheme 22: Deformylative Regitz diazo transfer.

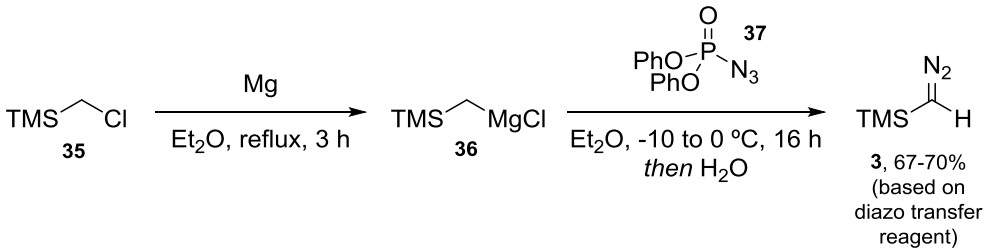
The diazo transfer method is not necessarily limited to carbonyl compounds. Starting from **32**, the precursor **33** was formed *via* a Claisen reaction, then generation of the stabilised α-diazophosphonate reagent **34** (Seyferth-Gilbert reagent) was conducted in moderate yield under analogous conditions to the aforementioned methods utilising carbonyl compounds as substrates (Scheme 23).[43]



Scheme 23: Synthesis of the Seyferth-Gilbert reagent (**34**) *via* Regitz diazo transfer.[43]

In addition, a Grignard reagent can be used in lieu of suitably acidic substrates; trimethylsilyldiazomethane (**3**) can be generated from the Grignard reagent (**36**) derived from

chloromethyltrimethylsilane (**35**), *via* reaction with the diazo transfer reagent diphenyl phosphorazidate (**37**) (Scheme 24).[44]



Scheme 24: Synthesis of trimethylsilyldiazomethane (**3**) by Regitz diazo transfer.[44]

1.3. Previous reports of flow-generated diazo compounds

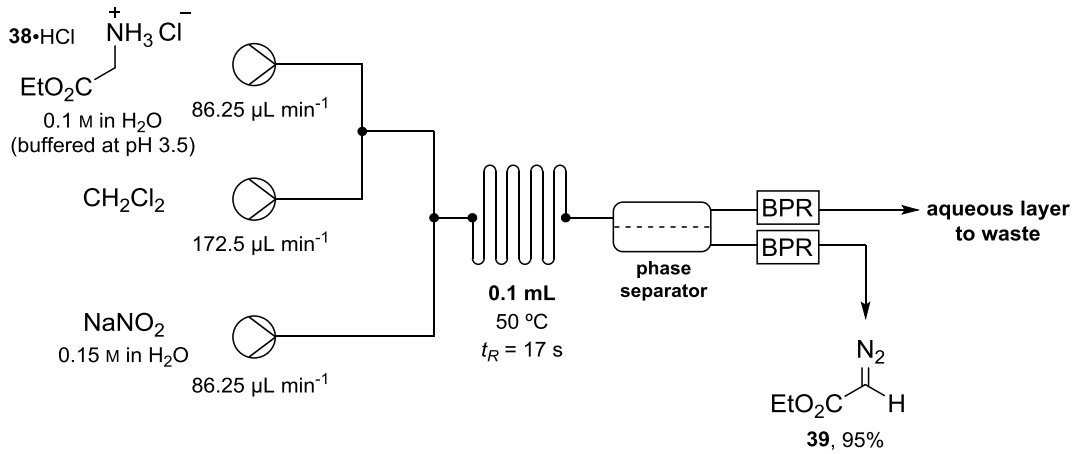
The inherent toxicity and explosive properties of diazo compounds present significant safety hazards for their use in chemical reactions, particularly for large-scale processes. Flow methods have therefore attracted substantial attention for the generation and use of diazo compounds.[45-47]

In these processes, the required diazo intermediate can be generated in small quantities from more stable precursors *in situ* and reacted in subsequent steps without any manual operator handling. In addition, scale up of these processes is safer as only a small amount of the hazardous diazo compound is present at any point in time. The desired product can be left to accrue over time, thus avoiding the generation of large quantities of reactive species in an analogous batch process.[47] Another advantage arises from the large surface area to volume ratio of reaction channels in a flow system, which leads to very efficient heat transfer.[48] This property can be exploited particularly for exothermic reactions, where thermal runaway could lead to uncontrolled decomposition or detonation of the diazo compound.

A selection of reports that involve the generation of diazo compounds using flow methods are presented below and are split into three categories, involving the generation of: (a) stabilised diazo compounds; (b) semi-stabilised diazo compounds; and (c) non-stabilised diazo compounds.

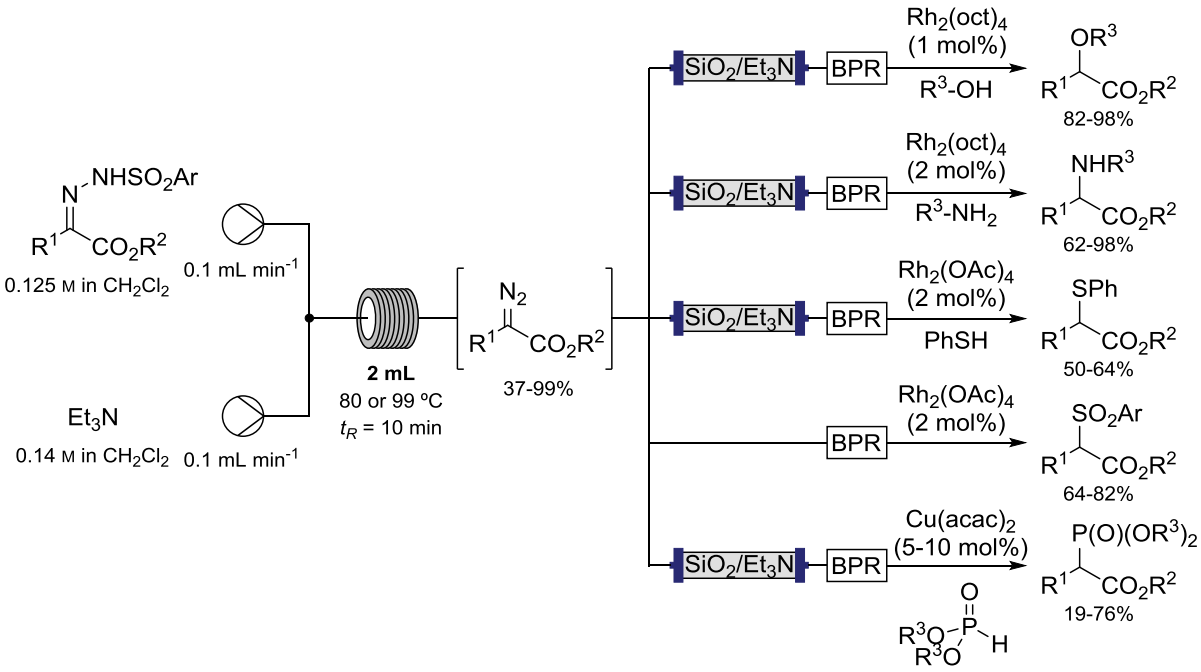
1.3.1. Flow-generated stabilised diazo compounds

Ethyl diazoacetate (**39**) represents a versatile two-carbon synthon in organic synthesis and hence, numerous reports have focused on its generation in a continuous flow fashion. Rutjes *et al.* investigated a method for the diazotisation of glycine ethyl ester hydrochloride (**38**•HCl) to form ethyl diazoacetate (**39**) in a microfluidic reactor.[49] Optimised conditions for this protocol involved passage of a buffered aqueous solution of glycine ethyl ester (**38**•HCl), 1.5 equiv. of sodium nitrite and CH_2Cl_2 through a microfluidic chip at 50 °C, followed by an in-line phase separation to provide solutions of **39** in 95% yield, with an overall production of approx. 20 g of ethyl diazoacetate per day (Scheme 25). Reports on the generation and use of **39** have also been demonstrated subsequently by Kim *et al.*[50] and Wirth *et al.*[51] in nucleophilic additions to aldehydes.



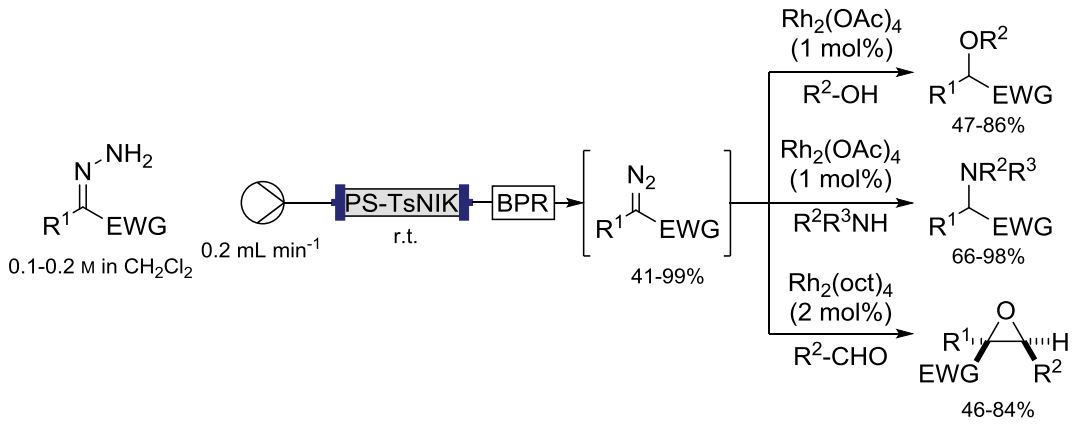
Scheme 25: Flow synthesis of ethyl diazoacetate (**39**) as reported by Rutjes *et al.*[49]

A different flow approach using the Bamford-Stevens reaction for the generation of stabilised α-diazoesters was reported by Hayes *et al.* – by passing solutions of sulfonylhydrazones and Et_3N through a heated reactor at 80 °C or 99 °C, moderate to excellent yields of their corresponding α-diazoesters were obtained.[52] These solutions could then be used for various heteroatom-H insertion reactions, for example metal-catalysed insertion into O-H, N-H, S-H and P-H bonds (Scheme 26).[52,53]



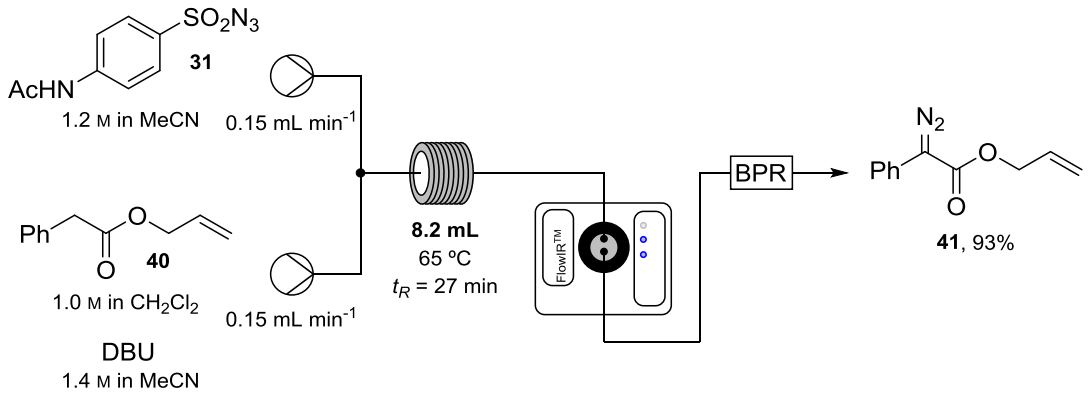
Scheme 26: Flow synthesis of α-diazoesters by the Bamford-Stevens reaction and their insertion reactions into heteroatom-H bonds as reported by Hayes *et al.*[52,53]

In 2015, Moody *et al*. showed that a polymer-supported version of *N*-iodo *p*-toluenesulfonamide potassium salt (PS-TsNIK)[54] could be utilised for the generation of various stabilised diazo compounds (α-diazocarbonyls and an α-diazophosphonate) from their corresponding hydrazones.[55] The reactor output provided sufficiently pure solutions of diazo compounds that could be immediately used for further derivatisation, for example in O-H and N-H insertion reactions, as well as epoxidation reactions (Scheme 27). A following report by Davies *et al*. showed that this flow oxidation method was also useful for enantioselective rhodium-catalysed C-H insertion reactions.[56]



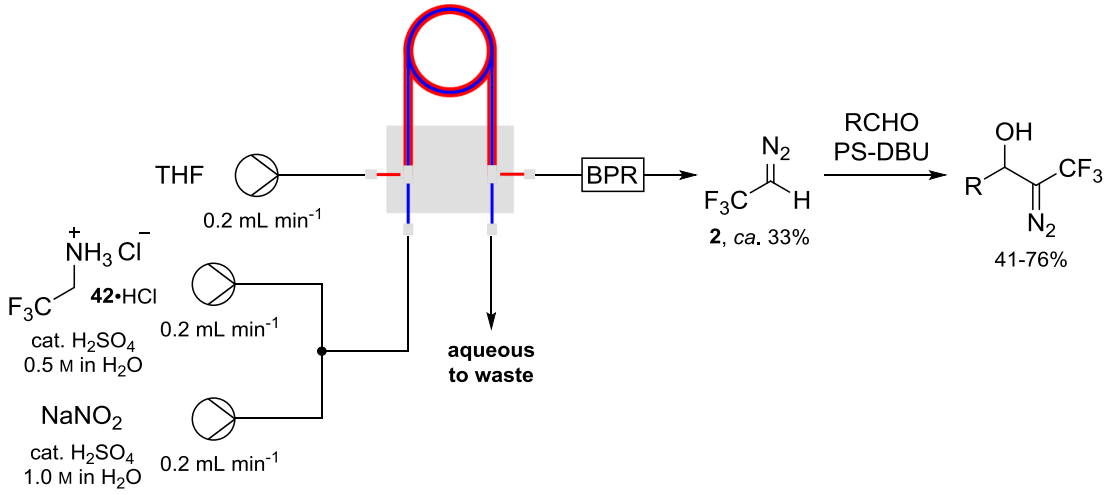
Scheme 27: Flow synthesis of stabilised diazo compounds *via* oxidation of hydrazones and their reactions with alcohols, amines and aldehydes as reported by Moody *et al.*[55]

Wirth *et al*. disclosed that α-diazoester **41** could be formed under flow conditions by Regitz diazo transfer using ester **40** and *p*-ABSA (**31**) (Scheme 28).[57] An initial analysis of differential scanning calorimetry data for **41** (onset temperature of 77 °C) indicated that if the exothermic enthalpy change associated with diazo transfer was not adequately controlled, thermal runaway would occur, thus highlighting the utility of a flow method for this process.



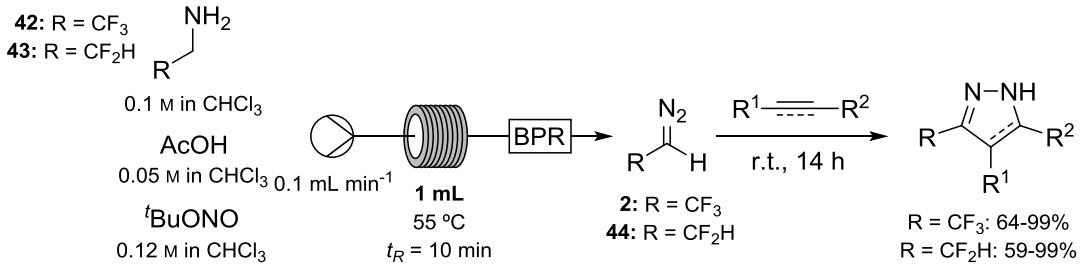
Scheme 28: Flow synthesis of α-diazoester **41** by Regitz diazo transfer as reported by Wirth *et al*.[57]

Other than α-diazocarbonyl compounds, the generation of (trifluoromethyl)diazomethane (**2**) and (difluoromethyl)diazomethane (**44**) in flow have also attracted interest. Pieber and Kappe[58] reported the use of the tube-in-tube reactor developed by Ley *et al*.[59] to access solutions of **2**, *via* diazotisation of amine hydrochloride **42**•HCl. Diffusion of the desired diazo compound **2** from the aqueous diazotisation solution in the inner tubing occurs through the gas-permeable membrane, into the outer tubing containing THF, thus providing solutions of **2** for further reactions. The use of this protocol was briefly illustrated by nucleophilic addition of **2** onto various aldehydes (Scheme 29).

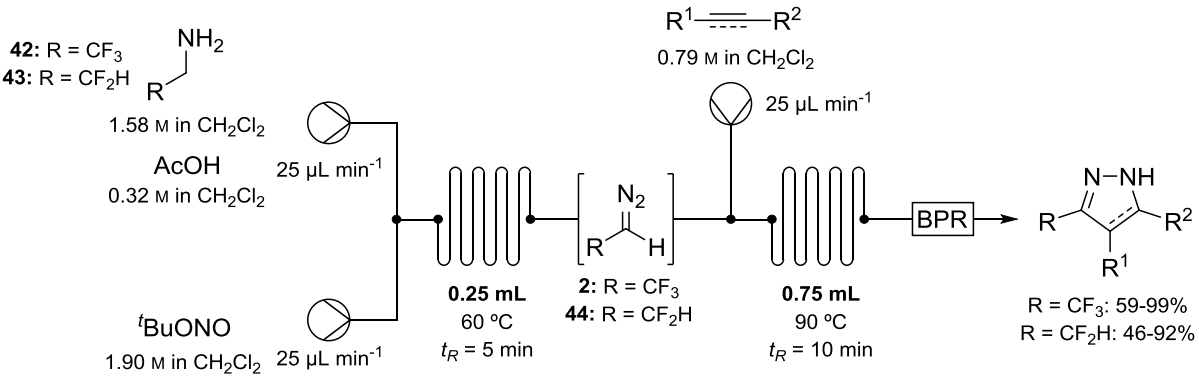


Scheme 29: Flow synthesis of (trifluoromethyl)diazomethane (**2**) by diazotisation as reported by Pieber and Kappe.[58]

Koenigs *et al.*[60,61] and Jamison *et al.*[62] have extensively investigated the formation of **2** and **44** in flow. In the first case, flow diazotisation of **42** or **43** with *tert*-butyl nitrite in the presence of acetic acid generates a solution of diazo compound **2** or **44**, which was then used in various batch mode [3 + 2] cycloadditions with alkenes and alkynes to form pyrazolines and pyrazoles respectively (Scheme 30). In the second, solutions of **2** or **44** were prepared analogously under flow conditions, but the [3 + 2] cycloadditions were also conducted in flow (Scheme 31).

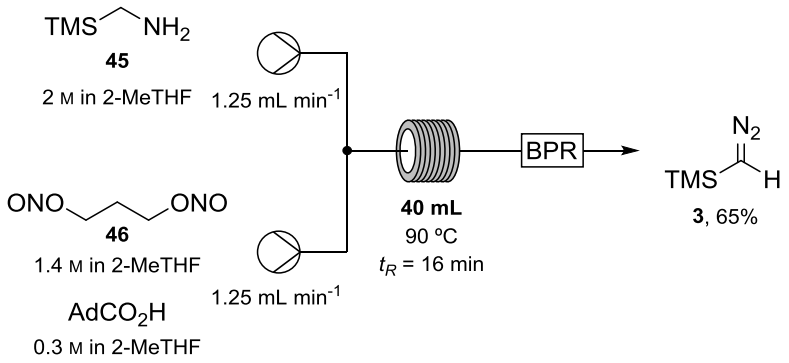


Scheme 30: Flow synthesis of **2** and **44** and subsequent [3 + 2] cycloaddition in batch as reported by Koenigs *et al.*[60,61]



Scheme 31: Flow synthesis of **2** and **44** and subsequent [3 + 2] cycloaddition in flow as reported by Jamison *et al.*[62]

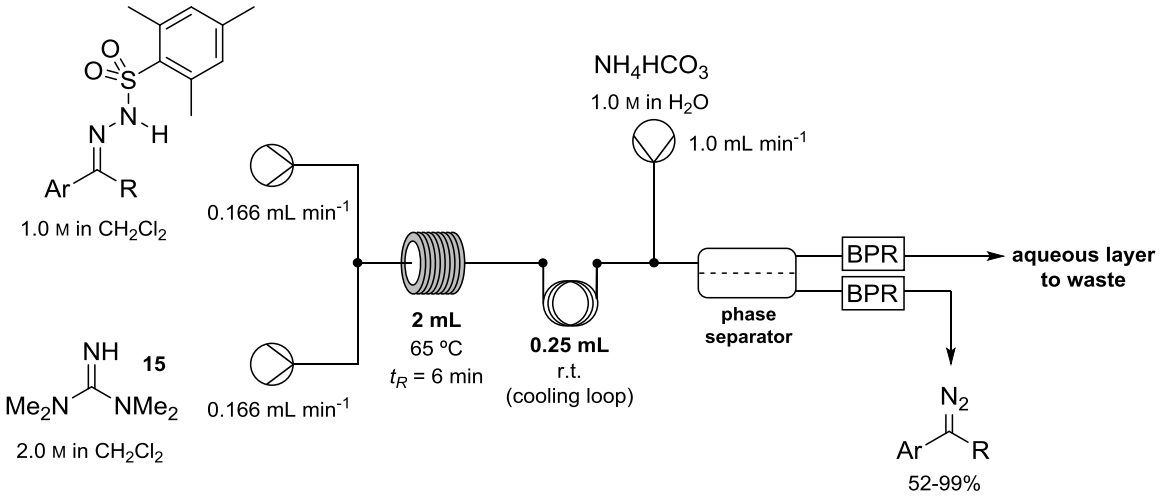
For stabilised silylated diazo compounds, a very recent report by Lebel *et al*. presented a route *via* diazotisation, for example using nitrite **46** to diazotise amine **45**, leading to the generation of trimethylsilyldiazomethane (**3**) in 65% yield (Scheme 32).[63]



Scheme 32: Flow synthesis of trimethylsilyldiazomethane (**3**) *via* diazotisation as reported by Lebel *et al.*[63]

1.3.2. Flow-generated semi-stabilised diazo compounds

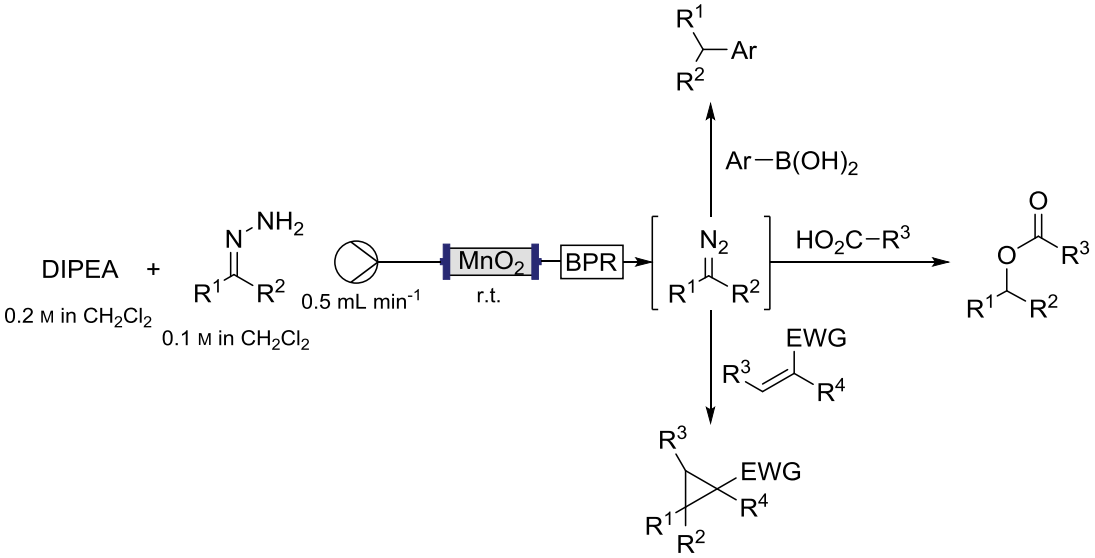
In contrast to stabilised diazo compounds, methods for the flow generation of semi-stabilised diazo compounds have only been recently developed. One possible flow method was presented by Charette *et al.* using the Bamford-Stevens reaction. Their report showed that passing a mixture of the mesitylsulfonylhydrazone with 2 equiv. of 1,1,3,3-tetramethylguanidine (**15**) through a heated reactor at 65 °C, followed by an in-line aqueous workup, leads to solutions of various aryldiazoalkanes (Scheme 33).[64] These precursors have lower decomposition temperatures than the more commonly used tosylhydrazones and thus facilitates the synthesis of semi-stabilised diazo compounds.



Scheme 33: Formation of semi-stabilised aryldiazoalkanes from mesitylsulfonylhydrazones under flow conditions as reported by Charette *et al.*[64]

Another approach using the oxidation of hydrazones was presented Ley *et al*. using flow methods.[65] When solutions of arylhydrazones with DIPEA were passed through columns of activated MnO_2, this allowed for the controlled generation of a variety of arylhydrazones

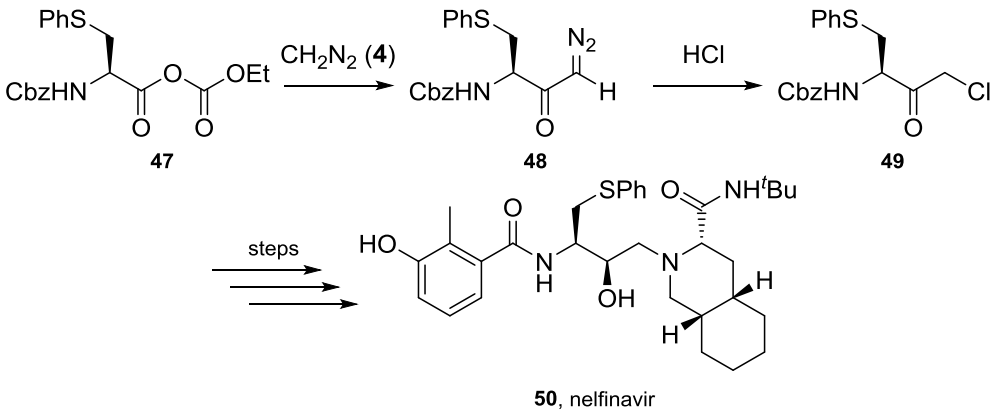
derived from aldehydes and ketones, as well as vinylhydrazones, which could be subsequently trapped with carboxylic acids,[65] boronic acids[65,66] (Chapter 4.1.2) and electron-deficient olefins (Scheme 34).[67]



Scheme 34: Formation of semi-stabilised diazoalkanes *via* oxidation of hydrazones under flow conditions as reported by Ley *et al*.[65-67]

1.3.3. Flow-generated non-stabilised diazo compounds

In 1998, the Aerojet-General Corporation filed a patent for the continuous flow generation of diazomethane (**7**) from *N*-methyl-*N*-nitrosourea, thus providing a method to safely generate tonne-scale quantities of ethereal solutions of **7**.[68] A later report in 2002 by Phoenix Chemicals Ltd. investigated the continuous flow generation of diazomethane (**7**) from Diazald® (**14**), to be used for the tonne-scale synthesis of α-chloroketone **49**, a key intermediate for the synthesis of the antiviral drug nelfinavir (**50**).[69] In this process, an initial attack of **7** on anhydride **47** leads to formation of the α-diazocarbonyl compound **48**, which can be subsequently treated with HCl to form **49** (Scheme 35).



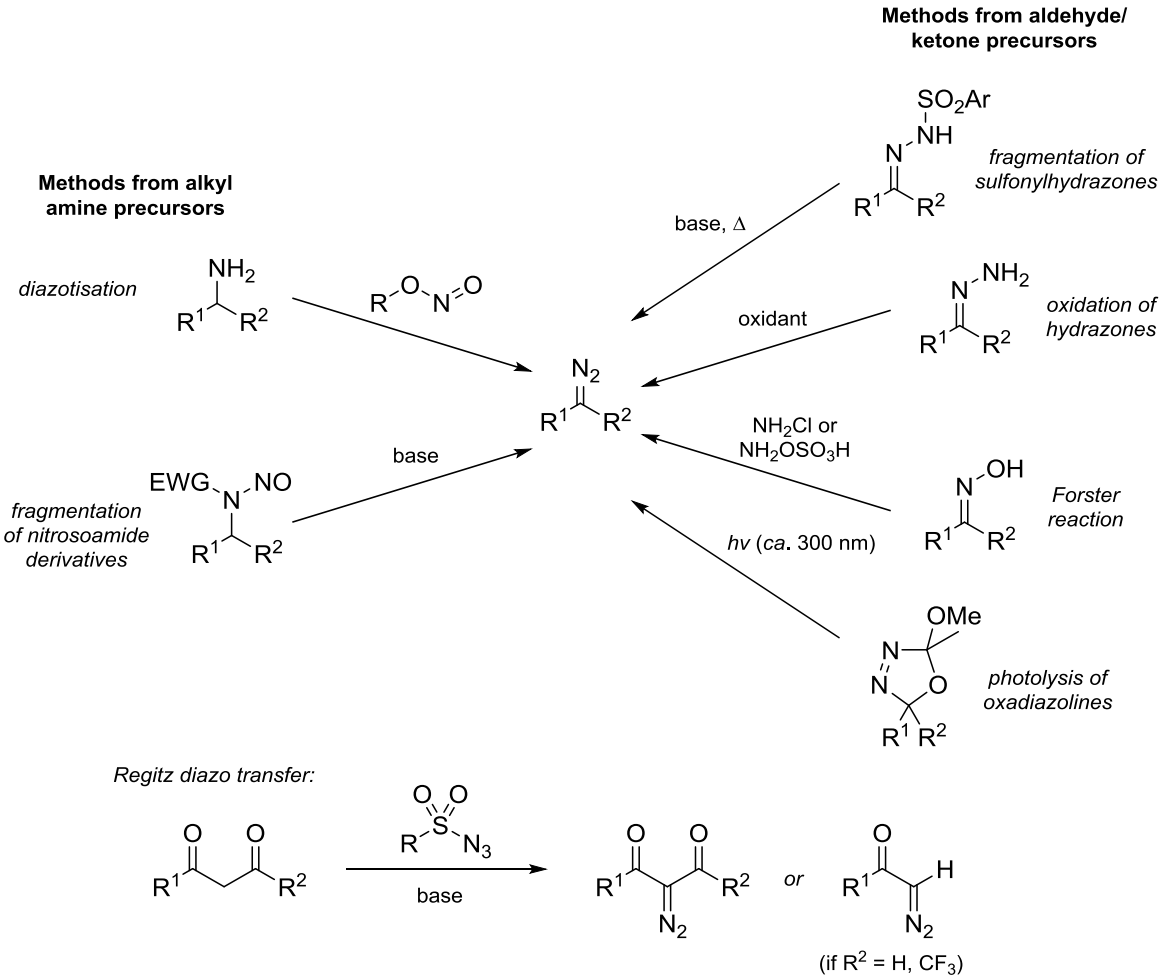
Scheme 35: Use of flow-generated diazomethane for the synthesis of intermediate **49**.[69]

A number of equivalent smaller scale procedures for the continuous flow preparation of diazomethane have been described since these seminal reports,[70-72] as well as examples utilising gas-permeable membranes.[73,74]

Whilst these flow methods have proven useful for safe handling of diazomethane, no reports have been disclosed for the flow generation of any other non-stabilised diazo compounds. This therefore represents a major unexplored area in diazo compound synthesis using flow chemistry.

1.4. Summary and project overview

A multitude of approaches for the synthesis of diazo compounds have been reviewed and are summarised below (Scheme 36). Although some of these methods have existed for a number of decades, precedent reports have primarily focused on the generation and use of stabilised diazo compounds. In contrast, mild procedures to access and utilise diazo compounds from the semi-stabilised and non-stabilised families still remain highly underdeveloped.



Scheme 36: Summary of synthetic routes for generation of diazo compounds.

One objective of this work thus focuses on the development of procedures that allow safe and mild generation of semi-stabilised and non-stabilised diazo compounds. It is hoped that the use of flow technologies could potentially facilitate this process. With methods in hand for forming these unstable species, it would then be possible to demonstrate their synthetic utility, with particular attention to their use in coupling reactions. Chapter 2 focuses on the synthesis of racemic allenes by coupling semi-stabilised diazo compounds with terminal alkynes, whilst Chapter 3 focuses on exploiting the mild generation of these diazo compounds for asymmetric allene synthesis. Finally, Chapter 4 describes the generation and use of non-stabilised diazo compounds in metal-free $C(sp^2)$-$C(sp^3)$ coupling reactions with arylboronic acids.

2. Racemic allene synthesis using flow-generated aryl diazo compounds

2.1. Properties of allenes

Allenes constitute the first member of the family of cumulenes, compounds containing consecutive carbon-carbon double bonds. Their two orthogonal cumulated double bonds have piqued the interest of chemists for over a hundred years, structures predicted initially by van't Hoff in 1874,[75] and then were first synthesised by Burton and von Pechmann in 1887 (glutinic acid, **51**).[76] Since their initial discovery, allenes have been historically considered to be 'chemical curiosities'. In the past few decades, however, there has been a resurgence of interest in their synthetic utility.[77-80] In addition, the allene moiety has been found in various natural products (e.g. isolaurallene, **52**) and incorporated into drugs (e.g. enprostil, **53**) and molecular materials (e.g. **54**) (Figure 4).[81,82]

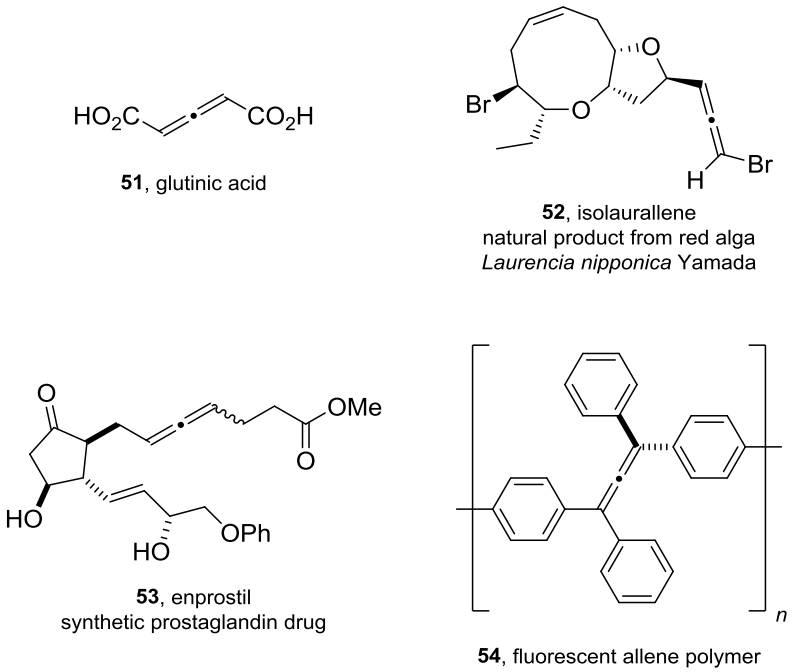


Figure 4: The allene moiety in natural products, drug molecules and functional materials.

In some cases, the higher reactivity of allenes compared to their alkene and alkyne counterparts provides complementary reaction pathways that can occur with higher selectivity and under milder reaction conditions.[79] In addition, the unique axially chiral nature of the allene skeleton allows the generation of multiple chiral centres under high stereocontrol, especially for cycloaddition and cyclisation reactions.[77-80]

Structurally, allenes can be considered to simply consist of two orthogonal π-bonds, with the two terminal carbon atoms being sp^2-hybridised and the central carbon atom sp-hybridised

(Figure 5). This simplified model, however, appears to be insufficient to explain the high levels of enantiocontrol in some [2 + 2] cycloaddition reactions; in reality, the frontier molecular orbitals of allenes are helical in nature.[83] For achiral allenes, the two HOMOs are degenerate orbitals, whereas for chiral allenes, this degeneracy is broken, resulting in a left-handed or right-handed helical HOMO depending on which enantiomer is being considered.

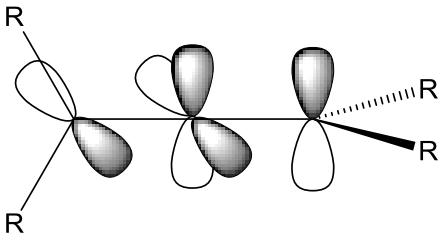
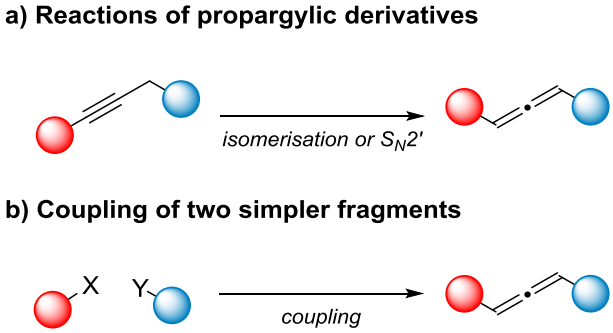


Figure 5: Simplified model of molecular orbitals in allenes.

2.2. Synthesis of allenes

Methods to synthesise allenes can be broadly categorised into two groups (Scheme 37): (a) reactions of propargylic derivatives to the corresponding allenes, *via* deprotonation or S_N2' displacement reactions; and (b) the coupling of two simpler fragments that results in the concomitant formation of one of the two C=C bonds in the allene skeleton.

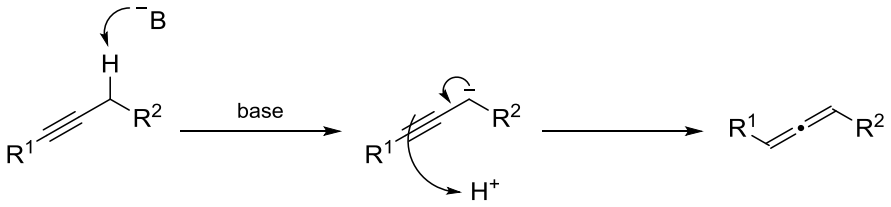


Scheme 37: Types of methods to access allenes.

2.2.1. Reactions of propargylic derivatives

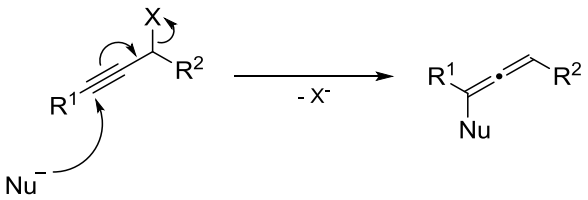
Isomerisation of propargylic derivatives is one of the most common methods to synthesise allenes. When one of the hydrogen atoms next to the alkyne is suitably acidic, it is possible to deprotonate this centre followed by a 1,3-protonation of the resulting anion, completing a formal prototropic rearrangement (Scheme 38).[77,84-86] Thus in the case of adjacent alkenyl or

aryl groups, for example, it is possible to deprotonate the methylene unit using a strong base, and thereby create a new π-bond that is in conjugation with the existing π-systems. For adjacent electron-withdrawing groups, such as carbonyl groups, sulfoxides, sulfones and phosphonates, isomerisation can be initiated under milder basic conditions due to the high acidity of the hydrogen atoms in the α-position. A variety of heteroatoms, including oxygen, nitrogen, sulfur, phosphorus and halogens, can also provide suitable acidity for the methylene unit, although similarly to the alkenyl/aryl case, a strong base is required to initiate deprotonation.[77]



Scheme 38: Deprotonation and reprotonation approach for allene synthesis.

An alternative method to derivatise propargylic derivatives is *via* a metal-mediated S_N2' reaction (Scheme 39), when a suitable leaving group is attached to the α-carbon of the alkyne skeleton. In particular, copper-mediated S_N2' processes are relatively common and versatile methods to access allenes; the choice of leaving group is broad, ranging from acetates, sulfonates, ethers, halides, epoxides and aziridines.[77] Although less popular, alternative processes are also viable, such as aluminium, indium, titanium, samarium and zirconium-mediated reactions.[77,84]



Scheme 39: S_N2' approach for allene synthesis.

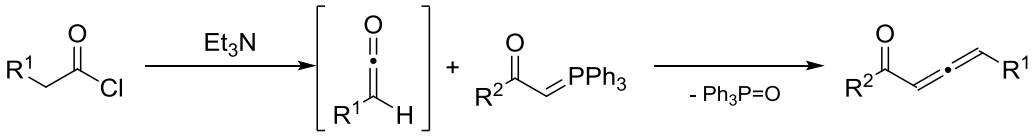
2.2.2. Coupling reactions of two simpler fragments

In comparison, the synthesis of allenes by coupling two fragments that results in the formation of one of the constituent π-bonds of the allene framework is more rarely described in the literature. However, in terms of rapidly building molecular complexity, these methods can be more valuable compared to the propargylic derivative route, as any complex molecular architecture must come preinstalled in the starting material for the latter case.

One approach reported by Barrett *et al*. involves the cross-metathesis of two mono-substituted allenes in the presence of Grubbs' catalyst (**55**), thus generating symmetrical disubstituted allenes (Scheme 40).[87] However, the method also produces significant levels of polymeric byproducts and thus limits its utility.

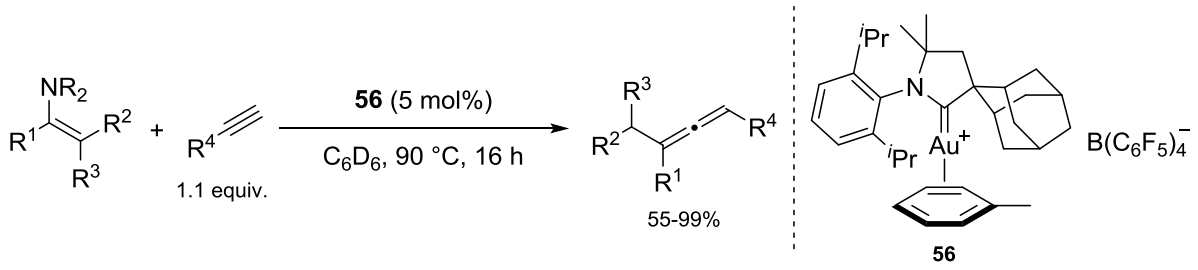
Scheme 40: Allene cross-metathesis to access symmetrical disubstituted allenes as reported by Barrett *et al*.[87]

A more general method proceeds *via* a Wittig reaction between phosphonium ylids and ketenes (formed *in situ* from the corresponding acyl chlorides in the presence of base), allowing access to allenyl esters, ketones and lactams (Scheme 41).[88]



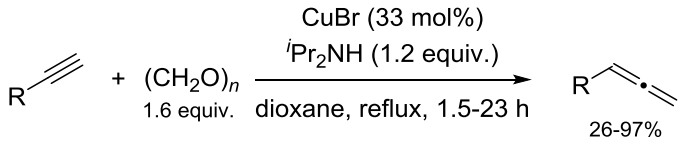
Scheme 41: Reaction of *in situ* generated ketenes with phosphonium ylids to generate allenes.

In 2007, Bertrand *et al*. reported the gold(I)-catalysed coupling of enamines and terminal alkynes using **56**, providing a variety of mono-, di- and trisubstituted allenes in moderate to excellent yields (Scheme 42).[89]



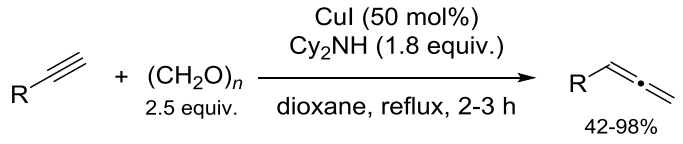
Scheme 42: Coupling of enamines with terminal alkynes using gold(I) catalysis as reported by Bertrand *et al.*[89]

One of the earliest methods to access allenes by coupling was reported in 1979 by Crabbé *et al.*, which occurs *via* a CuBr-mediated coupling of a terminal alkyne, paraformaldehyde and diisopropylamine (Scheme 43).[90]



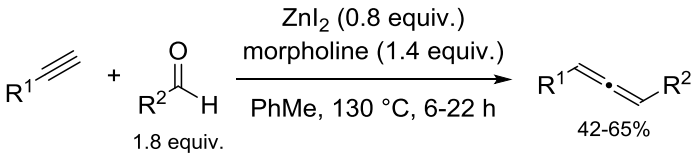
Scheme 43: Coupling of terminal alkynes with formaldehyde in the presence of diisopropylamine under CuBr catalysis as reported by Crabbé *et al.*[90]

Significant limitations of the original protocol included low-yielding reactions (although the yields were later improved by Kuang and Ma by using CuI and dicyclohexylamine instead, Scheme 44),[91] and the inability to utilise other aldehydes or ketones other than formaldehyde, hence only providing access to monosubstituted allenes.



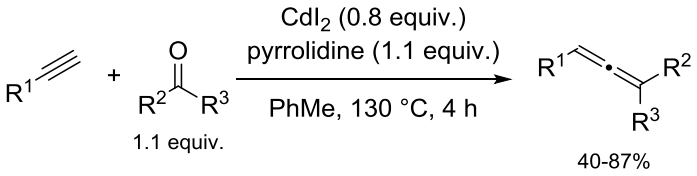
Scheme 44: Improved conditions for coupling of terminal alkynes with formaldehyde using CuI and dicyclohexylamine as reported by Kuang and Ma.[91]

Further work by Ma *et al.* found that by replacing the copper(I) salt with ZnI_2, aldehydes become permissible substrates for this method, thus providing a route to disubstituted allenes, although the high metal salt loading is a major drawback (Scheme 45).[92]



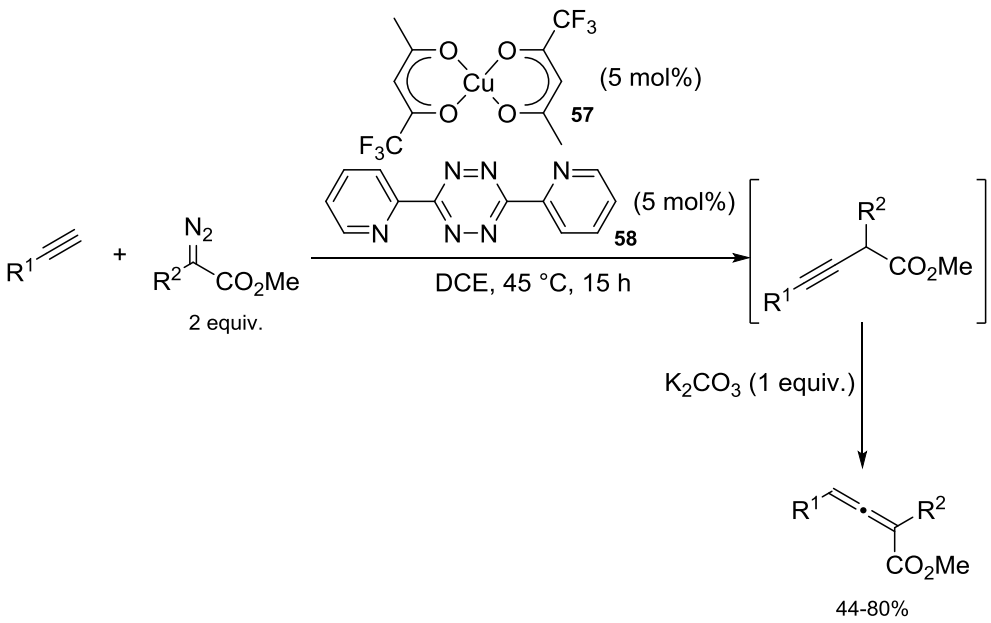
Scheme 45: Coupling of aldehydes with terminal alkynes using substoichiometric ZnI_2 for disubstituted allene synthesis as reported by Ma *et al.*[92]

In addition, ketones can also be utilised by replacing the metal salt with CdI_2, thus providing access to trisubstituted allenes. Again, the high metal salt loading combined with its acute toxicity is problematic (Scheme 46).[93]



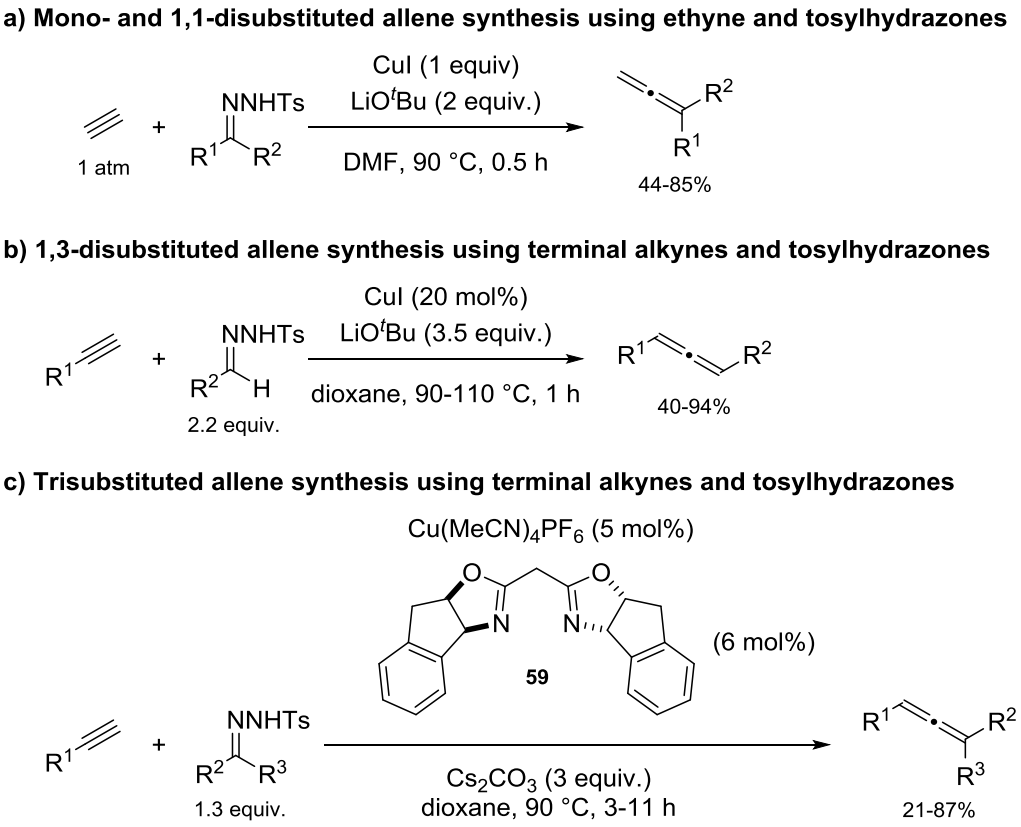
Scheme 46: Coupling of ketones with terminal alkynes using substoichiometric CdI_2 for trisubstituted allene synthesis as reported by Ma *et al.*[93]

The final coupling method for allene synthesis involves the coupling of diazo compounds and terminal alkynes. In 2011, Fox *et al*. reported the generation of allenes *via* coupling of stabilised α-diazoesters and terminal alkynes in the presence of base, copper(II) catalyst **57** and tetrazine-derived ligand **58** (Scheme 47).[94] The reaction mechanism appears to proceed *via* generation of the corresponding alkyne-coupled product as observed in a previous report by Suárez and Fu,[95] followed by a prototropic rearrangement (Section 2.2.1) of the initially formed alkynoate to the isomeric allenoate.



Scheme 47: Coupling of α-diazoesters with terminal alkynes using copper(II) catalysis as reported by Fox *et al.*[94]

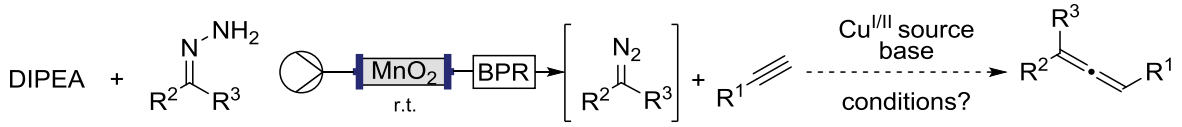
Wang *et al*. have also reported various conditions for the copper-mediated coupling of tosylhydrazones with terminal alkynes for the generation of mono-, di- and trisubstituted allenes, thus expanding the scope of this method to more unstable diazo compounds (Scheme 48).[96-98] For the latter case, ligand **59** was required to provide good yields of trisubstituted allenes.[98]



Scheme 48: Coupling of tosylhydrazones with terminal alkynes using copper(I) as reported by Wang *et al*.[96-98]

2.3. Aims of the project

Since a method to generate solutions of semi-stabilised aryldiazoalkanes under flow conditions was recently developed within our group,[65] it was envisaged that these compounds would be highly useful for copper-catalysed allene synthesis by coupling with terminal alkynes. Unlike the harsh conditions employed by Wang *et al*. using the Bamford-Stevens reaction,[96-98] these milder procedures for diazo generation could potentially allow the use of more sensitive substrates that do not tolerate high temperature and basic reaction conditions, leading to enhanced yields and substrate scope. Hence, the primary aim of this project is to optimise and assess the scope of such a process, coupling flow-generated semi-stabilised diazo compounds with terminal alkynes (Scheme 49).



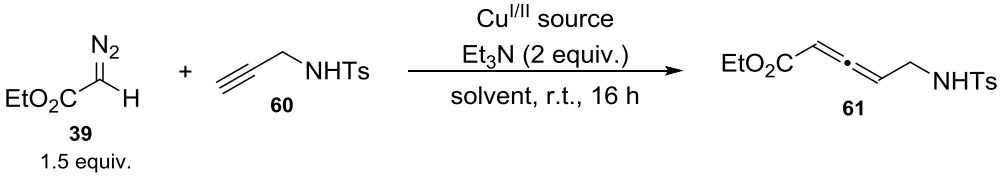
Scheme 49: Investigating the use of flow-generated semi-stabilised diazo compounds in allene synthesis.

2.4. Results and discussion

2.4.1. Initial results using ethyl diazoacetate

At the initial stage of investigations into allene formation using diazo compounds, it was desirable to find a set of alternative conditions to those obtained by Fox *et al*.[94] that would allow the analogous synthesis of allenes under milder conditions (i.e. ideally at room temperature), thus eventually permitting the generalisation of the scope to semi-stabilised diazo compounds prone to decomposition under the originally disclosed conditions. Using ethyl diazoacetate (**39**) and alkyne **60** as coupling partners, a variety of copper catalysts and loadings were tested, at room temperature for 16 h using triethylamine as the base.

Table 1: Optimisation for coupling of ethyl diazoacetate (**39**) and alkyne **60**.



Entry	Copper loading	Solvent	Yield* / %
1	10% CuOAc	dioxane	0
2	10% CuTC	dioxane	0
3	10% $Cu(acac)_2$	dioxane	0
4	10% CuF_2	dioxane	0
5	10% CuCl	dioxane	traces
6	10% CuBr•SMe_2	dioxane	31
7	**10% CuI**	**dioxane**	**84**
8	5% CuI	dioxane	63
9	20% CuI	dioxane	77
10	40% CuI	dioxane	77
11	10% CuI	PhMe	12
12	10% CuI	$PhCF_3$	21
13	10% CuI	CH_2Cl_2	42
14	10% CuI	THF	67
15	10% CuI	MeCN	42
16	10% CuI	MeOH	traces

* Reactions performed on 0.2 mmol scale with respect to alkyne **60**; yields stated are of isolated product.

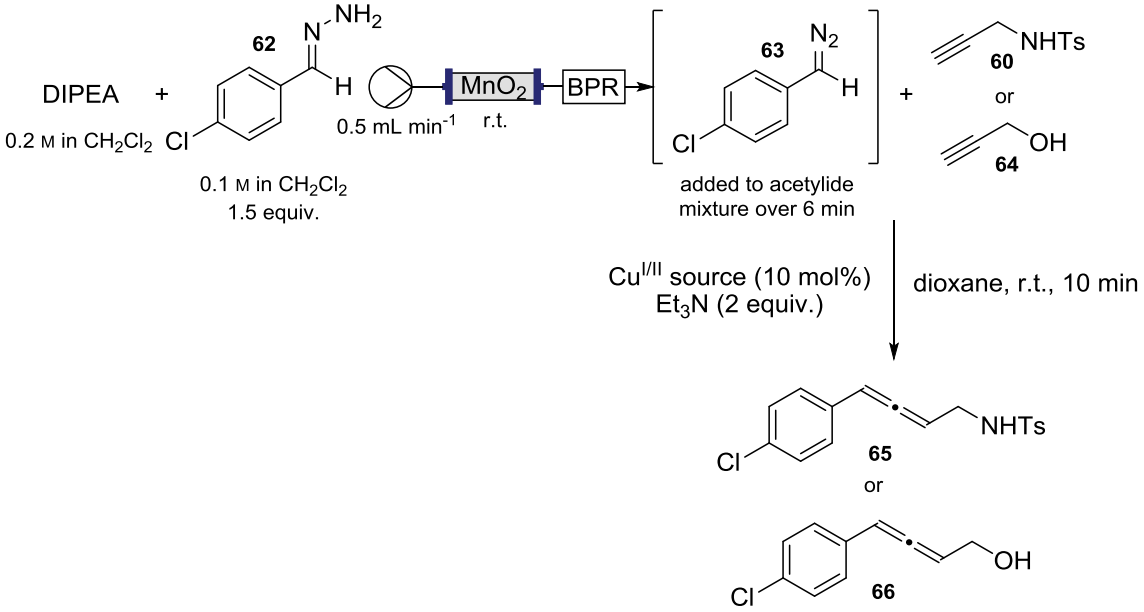
The majority of copper catalysts tested resulted in no conversion of alkyne **60** and decomposition of diazo compound **39**, including CuOAc, copper(I) thiophene-2-carboxylate (CuTC), $Cu(acac)_2$ and CuF_2 (Table 1, entries 1-4). With CuCl and $CuBr•SMe_2$, progressively higher yields of the allene product **61** were obtained (Table 1, entries 5 and 6), however CuI was found to be the ideal catalyst for the reaction, furnishing desired allene product **61** in 84% yield (Table 1, entry 7). Higher catalyst loadings than 10% of CuI (Table 1, entries 9 and 10) led to slightly lower yields of **61**, potentially due to increased rates of ethyl diazoacetate (**39**) decomposition, whereas a lowered loading of 5% CuI again led to reduced yield due to poorer conversion of starting material **60** (Table 1, entry 8).

The use of non-polar aprotic solvents (i.e. toluene) appeared to be vastly detrimental to the process (Table 1, entry 11), whereas in general increasing levels of polarity (from $PhCF_3$, MeCN, CH_2Cl_2 and THF) aided the reaction (Table 1, entries 12-15), with dioxane appearing to be optimal. The use of a polar protic solvent (MeOH) led to only traces of the desired product, presumably due to incompatibility of the *in situ* generated copper(I) acetylide with large quantities of protic solvent (Table 1, entry 16).

2.4.2. Using flow-generated aryl diazo compounds

With an optimised mild protocol for the generation of allenes from ethyl diazoacetate (**39**) and alkyne **60**, similar conditions were then attempted for the generalisation to semi-stabilised diazo compounds. Using hydrazone **62**, a solution of the hydrazone in CH_2Cl_2 with DIPEA as buffer was passed through a column of activated MnO_2 under flow conditions as described in previous literature.[65-67] This provided a solution of the corresponding diazo compound **63** which was added directly to the reaction mixture, using alkynes **60** and **64**. A similar screen of copper catalysts to the ones utilised for the coupling of ethyl diazoacetate showed a similar reactivity pattern with most being ineffective (Table 2, entries 1-5), and only CuI providing useful yields of the desired allene products **65** and **66** in 93% and 91% yield respectively (Table 2, entry 6). In sharp contrast to the initial studies using ethyl diazoacetate, the reaction of semi-stabilised diazo compound **63** with the copper(I) acetylide occurred much more rapidly, reaching full conversion within 10 min after addition of the diazo compound was complete, serving as testament to the enhanced nucleophilicity of semi-stabilised compounds when compared to stabilised ones.

Table 2: Copper salts tested for coupling of diazo compound **63** with alkynes **60** and **64**.

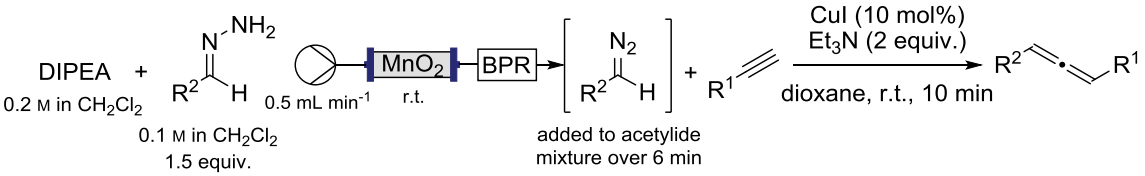


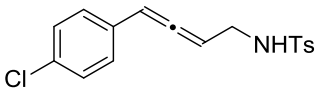
Entry	Copper salt	Yield of **65*** / %	Yield of **66*** / %
1	CuOAc	0	0
2	CuTC	0	0
3	$Cu(acac)_2$	0	0
4	CuF_2	0	0
5	CuCl	traces	traces
6	**CuI**	**93**	**91**

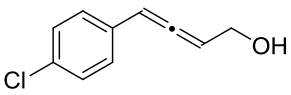
* Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product.

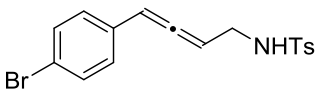
Having confirmed conditions for the coupling of semi-stabilised diazo compounds with alkynes, the scope of the reaction was then assessed (Scheme 50). A variety of diazo compounds derived from a selection of arylhydrazones were tested, including electron-deficient (**65-68**, **71**) and electron-rich (**69** and **70**) aromatic rings, all proceeding smoothly in excellent yields. A diazo compound derived from a vinylhydrazone was also tolerated (**72**), however a lower yield of 48% was obtained due to lower yielding diazo generation arising from cyclisation of the diazo compound to the corresponding pyrazole.[21] The scope of the alkyne component was screened extensively and revealed a vast compatibility with many functional groups as a result of mild coupling and diazo compound generation conditions, including alkyl and aryl alkynes (**73-75**), olefins (**76**), mono-protected amines (**77**), alkyl bromides and iodides (**78-80**), acetals (**81**), epoxides (**82**), nitriles (**83**), ferrocene (**84**) and unprotected alcohols (**85-88**), again all proceeding in high yields. For compounds with existing stereocentres (e.g. **82**, **86** and **87**), no diastereoselectivity was observed, likely due to

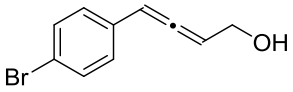
the remote nature of the new axially chiral centre with respect to existing chiral centres, thus highlighting the importance of establishing enantioselective methods to access chiral allenes (Chapter 3).

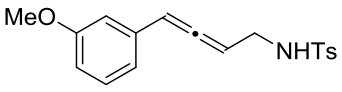


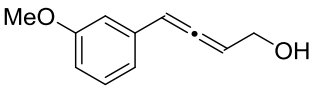

65, 93%


66, 91%


67, 92%


68, 99%


69, 81%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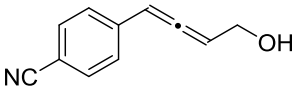
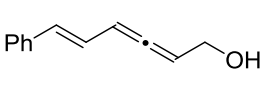
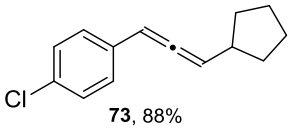
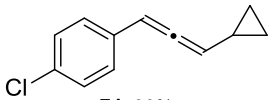

71, 83%


72, 48%


73, 88%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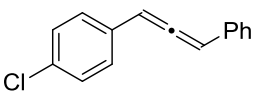
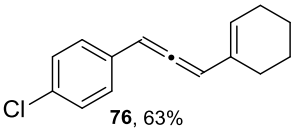

75, 92%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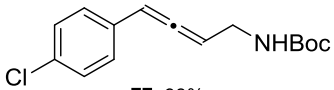
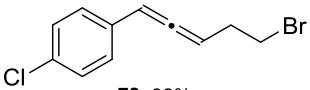
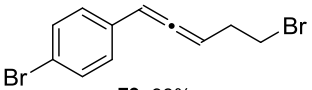
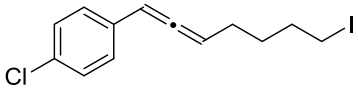
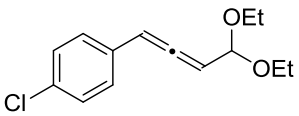
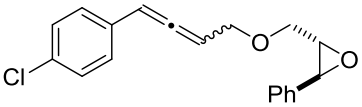

77, 93%

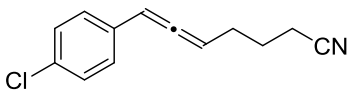

78, 82%

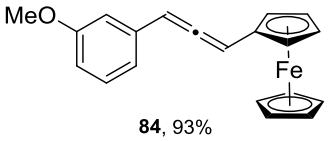

79, 93%

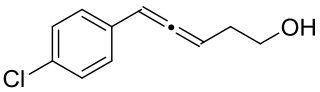

80, 93%

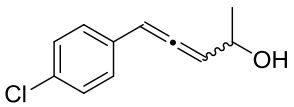

81, 99%

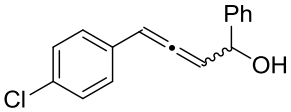

82, 89%, 1:1 *dr*

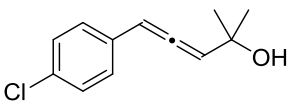

83, 93%


84, 93%


85, 93%


86, 83%, 1:1 *dr*

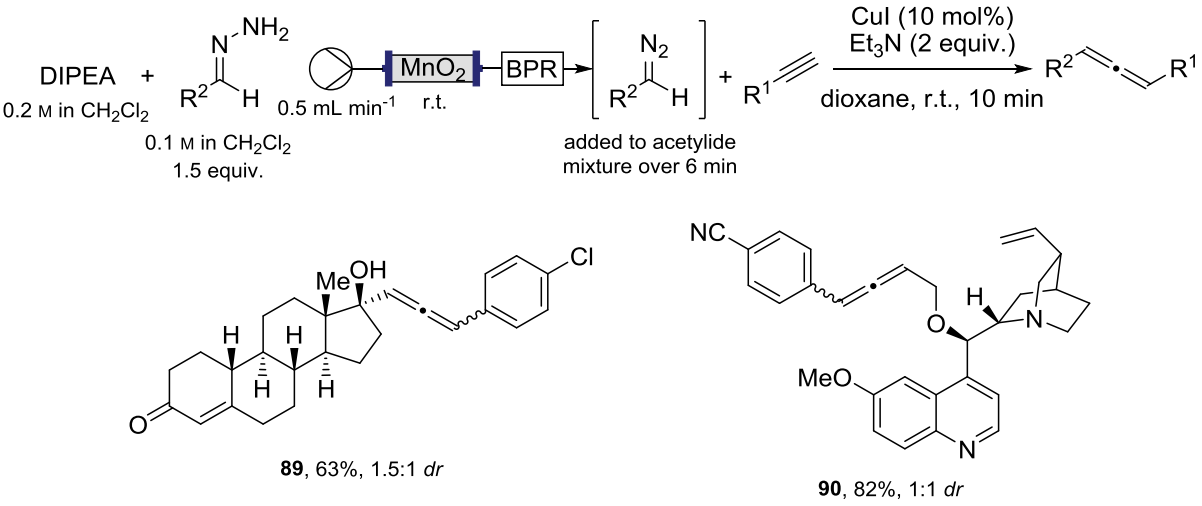

87, 97%, 1:1 *dr*


88, 82%

Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product; diastereomeric ratios determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 50: Disubstituted allene synthesis *via* coupling of aldehyde-derived semi-stabilised diazo compounds and terminal alkynes using CuI catalysis.

To illustrate the utility of the procedure, late-stage modification of the natural products/drug molecules norethindrone and a propargylated version of quinine were additionally investigated (Scheme 51). Coupling of diazo compound **63** with norethindrone provided the desired diastereomeric allenes **89** in 63% yield. Despite the presence of copper(I) intermediates during the reaction process, no Michael addition was observed at the enone functionality. Although the propargylated quinine derivative contains several functionalities that could pose problems (quinoline and tertiary amine leading to metal catalyst poisoning; terminal olefin undergoing cyclopropanation side-reactions), the desired diastereomeric allenes **90** were provided in a high yield of 82%.



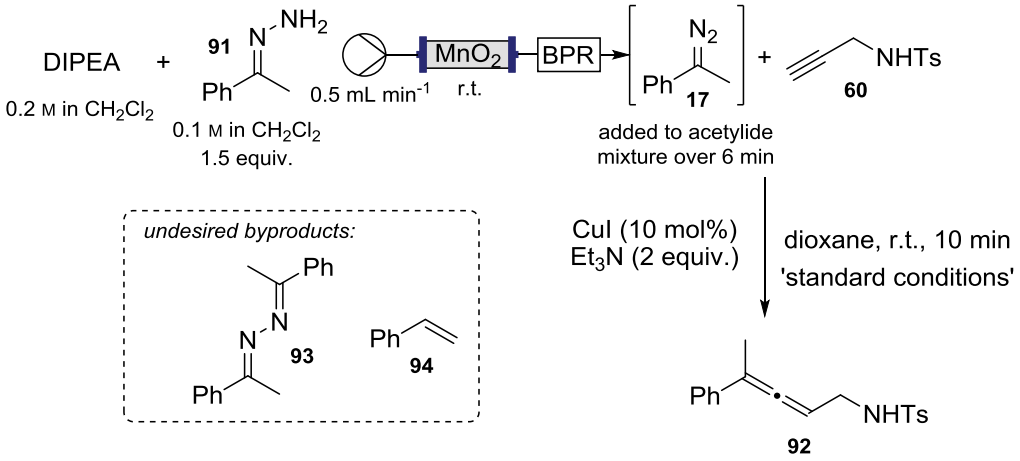
Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product; diastereomeric ratios determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 51: Late-stage modification of natural products/drug molecules.

An initial attempt at using arylhydrazones derived from ketones rather than aldehydes for trisubstituted allene synthesis resulted only in 25% yield of allene **92**, when acetophenone hydrazone (**91**) was used as the diazo compound precursor (Table 3, entry 1). In this case, the major side-products observed were diazine **93** and the alkene (styrene, **94**), resulting from metal-catalysed decomposition of diazo compound **17**. Utilising a stoichiometric quantity of CuI provided only little benefit to the reaction, raising the yield of **92** to 38% (Table 3, entry 2); whereas attempts at slow addition of the diazo compound over 2 h and 4 h provided slightly better results (44% and 43% yields respectively, Table 3, entries 3 and 4). Using NaI as an additive also was beneficial (Table 3, entry 5), potentially by regeneration of an active CuI catalyst when several turnovers of the copper(I) species have occurred. Inspired by

previous reports accessing trisubstituted allenes utilising ligands (Fox *et al.* used tetrazine ligand **57**, whereas Wang *et al.* used BOX ligand **58**),[94,96] it was found that 20 mol% 2,6-lutidine as an additive allowed the generation of allene **92** in 67% yield under analogous conditions to the disubstituted allene method (Table 3, entry 6), without the requirement for slow addition of diazo compound **17** or stoichiometric quantities of CuI.

Table 3: Optimisation for coupling of ketone-derived diazo compound **17** with alkyne **60**.



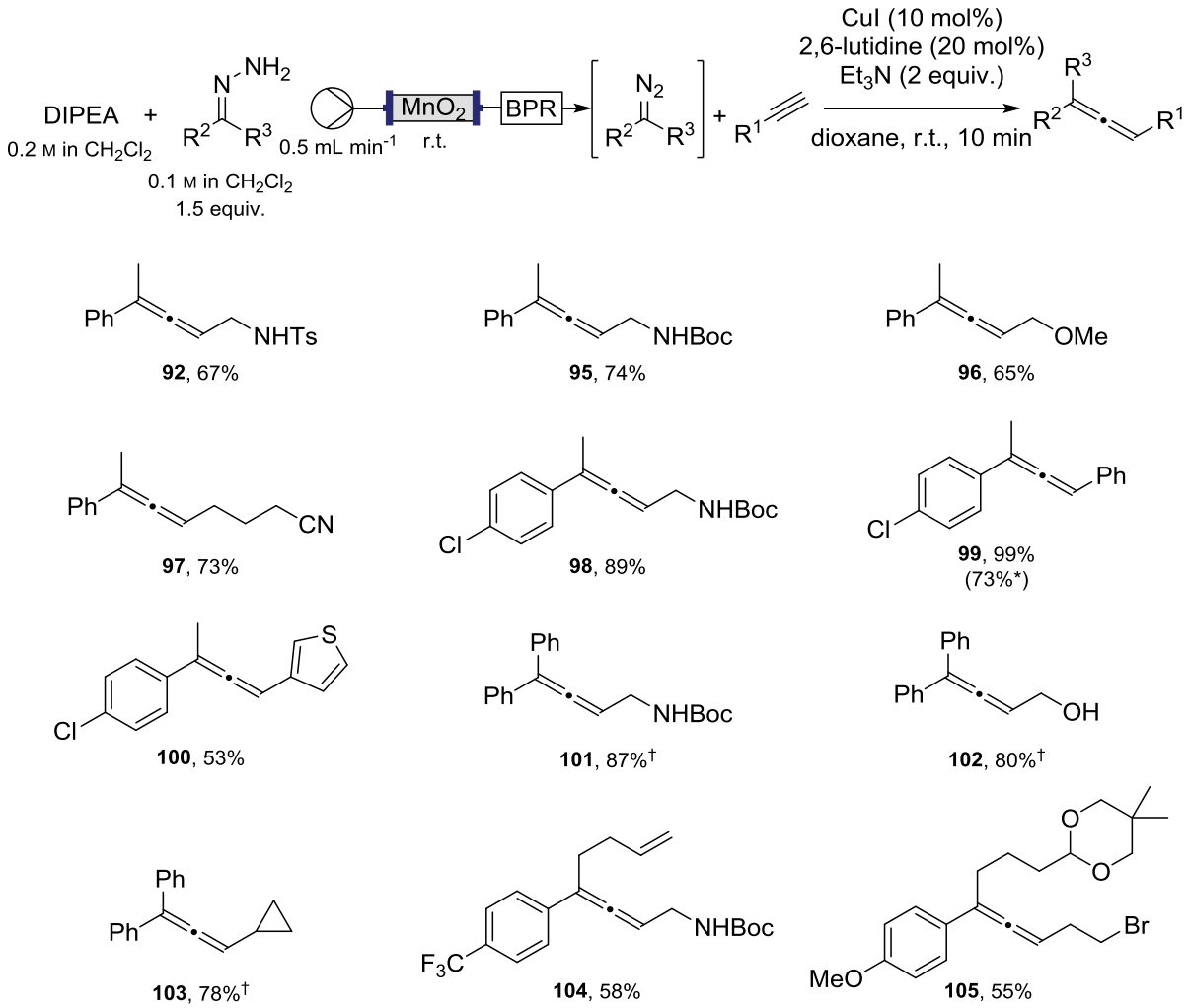
Entry	Deviation from standard conditions	Yield* / %
1	-	25
2	1 equiv. CuI	38
3	**17** (from 1.5 equiv. of **91**) added over 2 h	44
4	**17** (from 3 equiv. of **91**) added over 4 h	43
5	0.5 equiv. NaI	43
6	**20 mol% 2,6-lutidine**	**67**

* Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product.

Thus, with a modified method for the generation of trisubstituted allenes the scope of this method was investigated with a similar set of diazo compounds and alkynes (Scheme 52).[†] Again, both electron-deficient (**98-100**, **104**) and electron-rich (**105**) aromatic rings were suitable, including diaryl-substituted diazo compounds (**101-103**), providing moderate to excellent yields. In the case of allenes **104** and **105**, more significant decomposition of the diazo compound to the corresponding alkenes was observed, leading to lower yields of the desired products. A similar level of functional group tolerance in the alkyne component was obtained, allowing coupling with mono-protected amines (**92**, **95**, **98**, **101** and **104**), ethers (**96**), nitriles (**97**), thiophene (**100**), unprotected alcohols (**102**) and alkyl bromides (**105**). In

[†] This work was conducted in collaboration with Dr Duc N. Tran.

the case of allene **100**, the presence of thiophene could slightly inhibit copper(I) catalysis, leading to a lower yield compared to allenes **98** and **99**. Scale-up to 5 mmol of phenylacetylene provided 0.88 g of the allene **99**, though at a slightly reduced yield of 73% compared to 99% for the smaller scale run. This lower yield was attributed to less efficient diazo generation using a larger MnO_2 column, which led to greater decomposition of the diazo compound to its corresponding diazine and alkene.

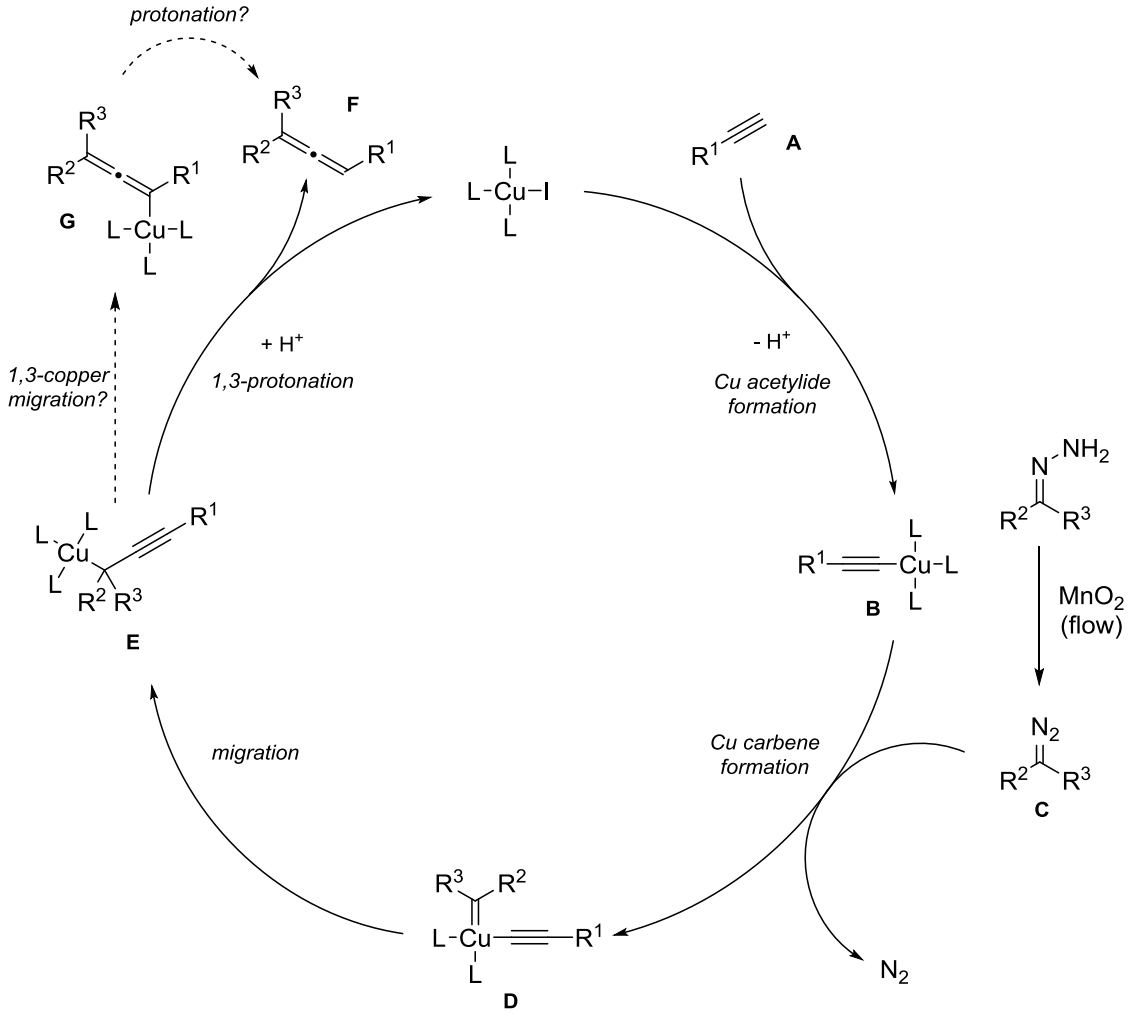


Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product.
* Reaction conducted on 5 mmol scale with respect to terminal alkyne. † Using 2 equiv. of hydrazone.

Scheme 52: Trisubstituted allene synthesis *via* coupling of ketone-derived semi-stabilised diazo compounds and terminal alkynes using CuI catalysis and 2,6-lutidine additive.

2.4.3. Mechanistic discussion

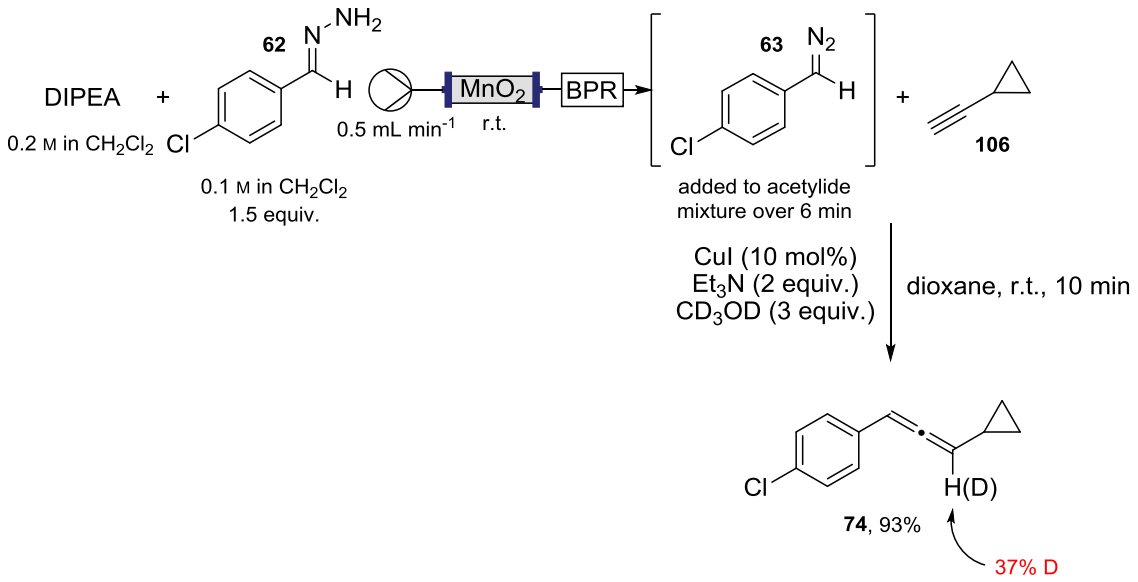
Mechanistically, it is thought that under copper(I) catalysis and basic conditions, the corresponding copper(I) acetylide **B** is generated from the terminal alkyne starting material **A**, followed by copper carbene formation (**D**) with the diazo compound (**C**). A subsequent migration leads to the generation of propargyl copper species **E**. 1,3-Protonation of propargyl copper species **E** thereby leads to regeneration of the copper(I) catalyst, generation of the desired allene cross-product **F** and completes the catalytic cycle (Scheme 53).



Scheme 53: Proposed mechanism for allene formation *via* copper-catalysed coupling of diazo compounds and terminal alkynes.

When the coupling reaction for cyclopropylacetylene (**106**) and diazo compound **63** was conducted in the presence of 3 equiv. deuterated methanol, 37% deuterium was incorporated into the C3-position of allene **74** (Scheme 54), which initially appeared to be evidence for the allenyl copper species **G**. However, based on more recent results (see Section 3.3.6), it

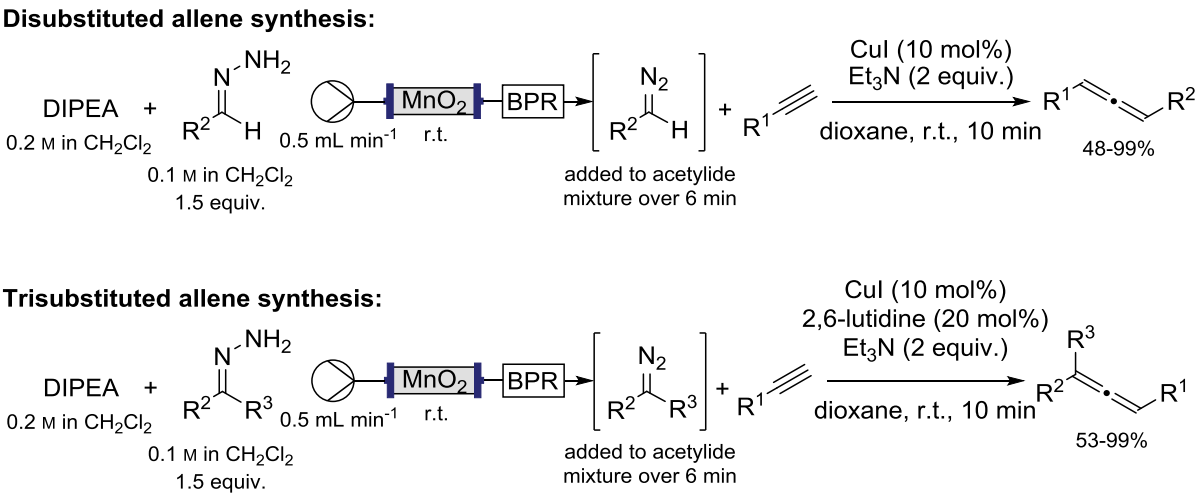
appears that proton-deuterium exchange with Et_3NH^+, followed by a 1,3-deuteration of the propargyl copper species is a more likely pathway.



Scheme 54: Formation of allene **74** in the presence of CD_3OD.

2.5. Conclusions and outlook

In summary, a versatile method for the generation of both disubstituted and trisubstituted allenes from the coupling of terminal alkynes and semi-stabilised diazo compounds has been developed (Scheme 55), exhibiting broad scope on both the diazo compound component and the alkyne component, in addition to moderate to high yields and fast reaction times.



Scheme 55: Summary of di- and trisubstituted allene synthesis by coupling of flow-generated semi-stabilised diazo compounds and terminal alkynes.

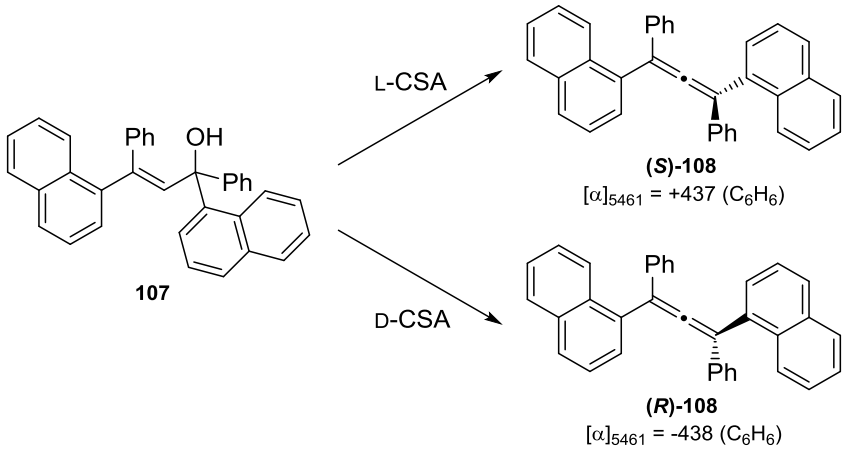
A variety of functional groups were tolerated under these mild reaction conditions, as well as being applicable to the late-stage functionalisation of two natural products/drug substances. Compared with previous routes towards allenes, this methodology represents a significant advance for allene synthesis, providing a mild, simple route to di- and trisubstituted allenes. This procedure should therefore enable easier access to these valuable intermediates and hence stimulate further research into the applications of allenes in organic synthesis.

With the racemic method proceeding smoothly at room temperature and promising results that ligands have a significant effect on reaction outcome (as observed for 2,6-lutidine being useful for trisubstituted allene synthesis), these initial findings set the foundation for the development of a new catalytic asymmetric coupling method to access chiral disubstituted allenes (Chapter 3).

3. Asymmetric disubstituted allene synthesis using flow-generated diazo compounds

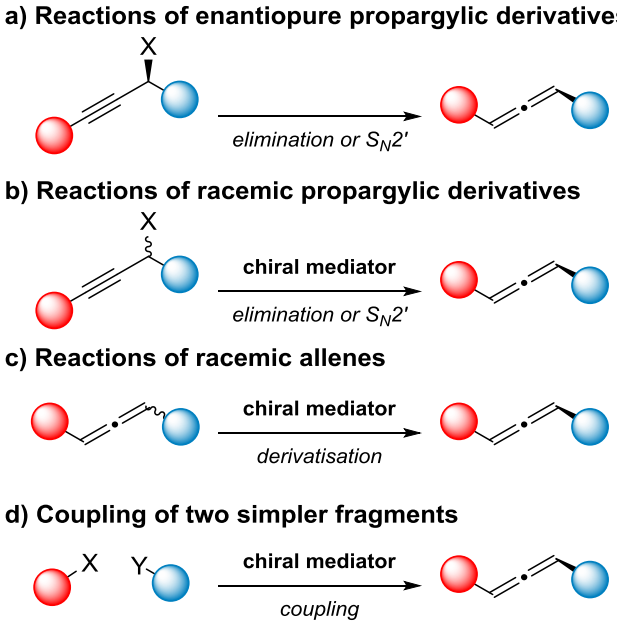
3.1. Asymmetric syntheses of allenes

The first synthesis of a chiral allene **108** was conducted by Maitland and Mills in 1935 *via* dehydration of the corresponding allylic alcohol **107**, in the presence of L- or D-camphorsulfonic acid (Scheme 56).[99,100]



Scheme 56: First synthesis of chiral allene **108** as reported by Maitland and Mills.[99,100]

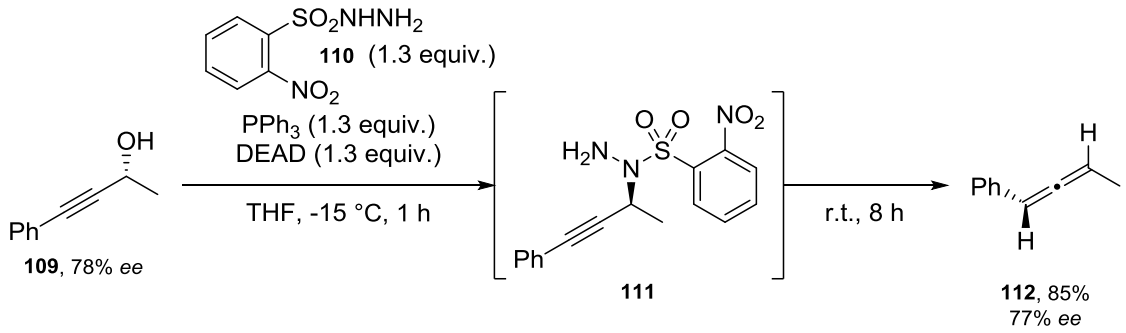
Since this original report, various methods have now been developed to access enantiopure allenes.[77,85] Like methodologies generating racemic allenes, chiral allenes can generally be accessed *via* reactions of enantiopure propargylic derivatives (using elimination or S_N2' displacement reactions), catalytic asymmetric reactions of racemic propargylic derivatives, or *via* asymmetric coupling reactions of two simpler fragments. In addition to these three classes, a fourth class can be considered, utilising racemic allene starting materials and subsequent asymmetric derivatisation (Scheme 57).



Scheme 57: Types of methods to access chiral allenes.

3.1.1. Reactions of enantiopure propargylic derivatives

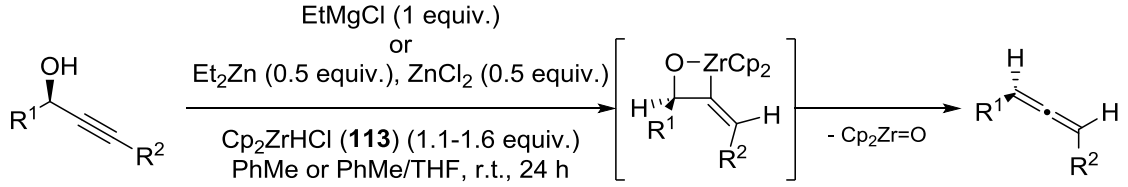
The derivatisation of enantiopure propargylic compounds is the most popular method to generate chiral allenes, generally due to easily accessible chiral starting materials. In 1996, Myers and Zhang reported a method to access chiral disubstituted allenes *via* a Mitsunobu reaction of chiral propargyl alcohols (e.g. **109**) with *o*-nitrobenzenesulfonylhydrazine (**110**) (Scheme 58).[101] Spontaneous elimination from intermediate **111** results in the stereoselective transformation of propargyl alcohol **109** to the desired allene **112**.



Scheme 58: Stereoselective elimination of propargyl alcohols under Mitsunobu conditions as reported by Myers and Zhang.[101]

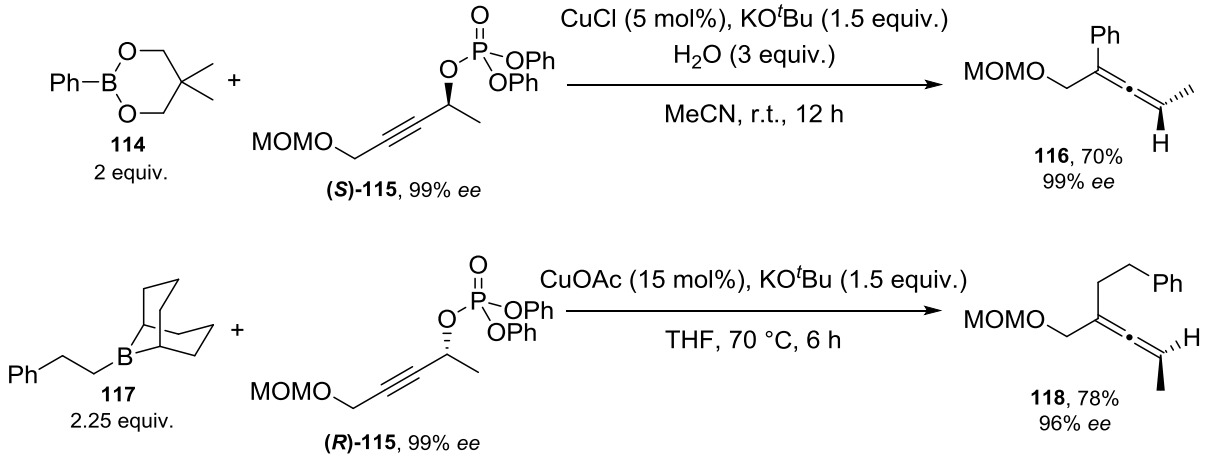
An analogous approach proceeding *via* elimination from propargyl alcohols utilises Schwartz's reagent (**113**), reported by Pu and Ready in 2008.[102] After deprotonation with EtMgCl or Et_2Zn, directed hydrozirconation of the internal alkyne produces a vinylzirconium

species, followed by rapid elimination to form the corresponding allene stereoselectively (Scheme 59).

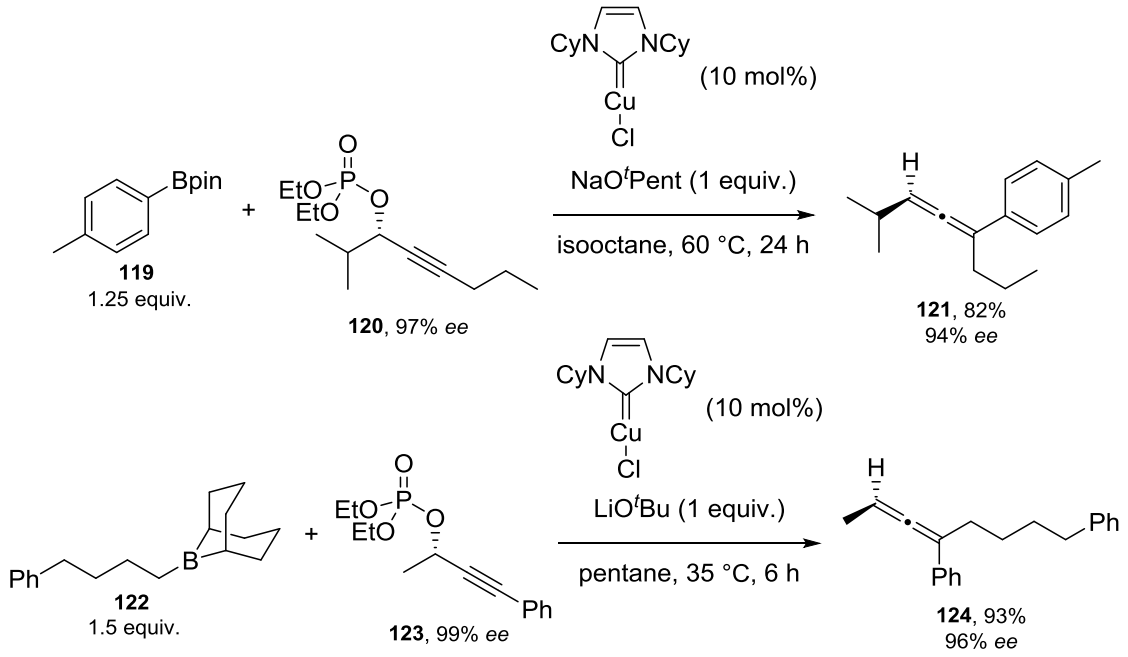


Scheme 59: Stereoselective elimination from propargyl alcohols using Schwartz's reagent (**113**) as reported by Pu and Ready.[102]

Approaches using S_N2'-type reactions have held significant interest in particular and existing methods typically proceed under copper-, palladium- or rhodium-mediated catalysis. Sawamura *et al*. (Scheme 60) and Lalic *et al*. (Scheme 61) have reported complementary copper-catalysed processes, reacting propargylic phosphates (e.g. **115**, **120**, **123**) with either aryl- (e.g. **114**, **119**) or alkylboron (e.g. **117**, **122**) derivatives to form chiral allenes (e.g. **116**, **118**, **121** and **124**).[103-105]

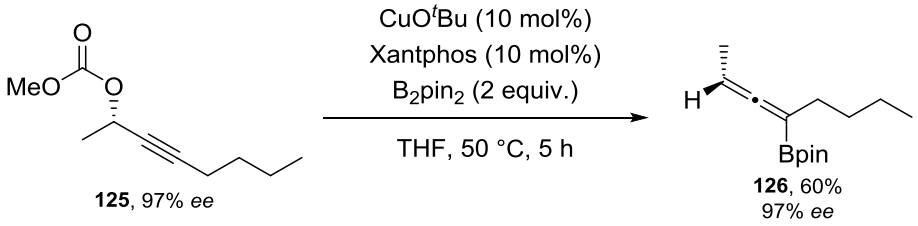


Scheme 60: S_N2'-type copper-catalysed reactions of chiral propargyl phosphonates with aryl- and alkylboron reagents as reported by Sawamura *et al*.[103,104]



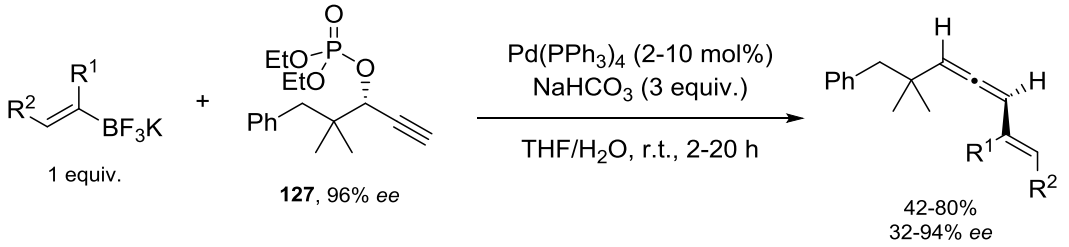
Scheme 61: S_N2'-type copper-catalysed reactions of chiral propargyl phosphonates with aryl- and alkylboron reagents as reported by Lalic *et al.*[105]

In addition, in 2008, Sawamura *et al*. disclosed a stereoselective substitution of propargylic carbonates (e.g. **125**) with bis(pinacolato)diboron, providing access to chiral allenylboronates (e.g. **126**) (Scheme 62).[106]

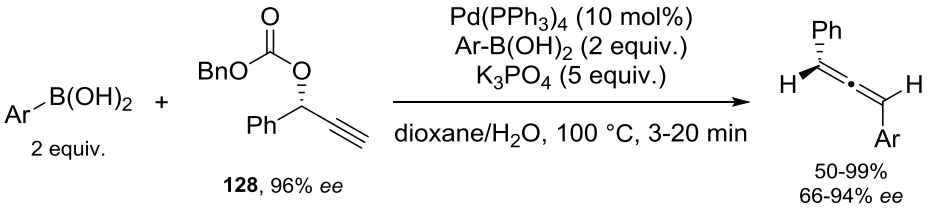


Scheme 62: S_N2'-type copper-catalysed reaction of chiral propargyl carbonate **125** to form chiral allenylboronate **126** as reported by Sawamura *et al.*[106]

For palladium-mediated catalysis, Molander *et al*. (Scheme 63) and Yoshida *et al*. (Scheme 64) have shown that propargylic phosphonates (e.g. **127**) and carbonates (e.g. **128**) can undergo S_N2'-type reactions, with alkenyl trifluoroborate salts and arylboronic acids respectively.[107,108] However, the scope of these two processes was limited and the degree of chirality transfer was highly variable.

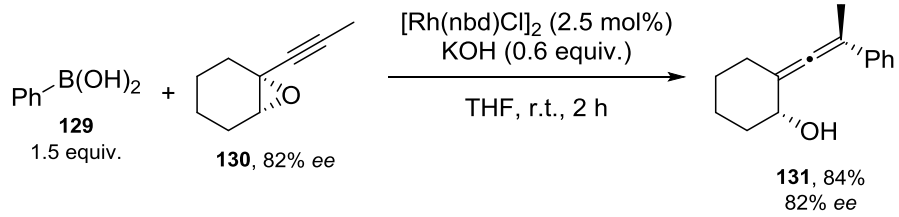


Scheme 63: S_N2'-type palladium-catalysed reaction of chiral propargyl phosphonate **127** with alkenyl trifluoroborate salts as reported by Molander *et al*.[107]



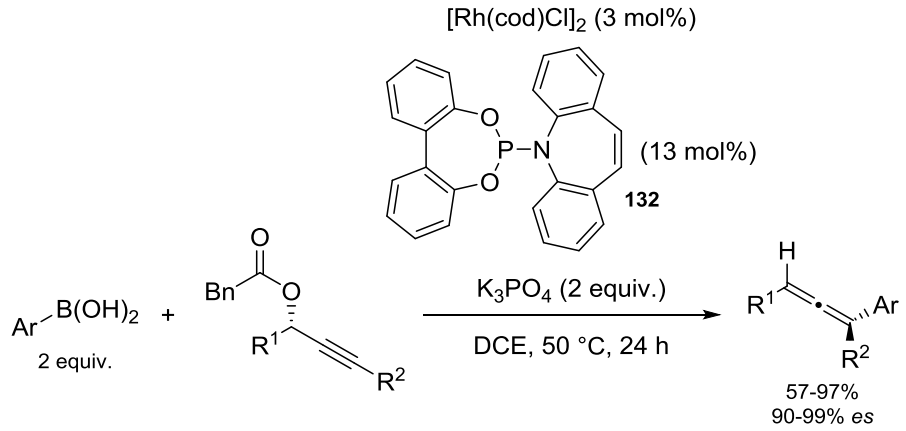
Scheme 64: S_N2'-type palladium-catalysed reaction of chiral propargyl carbonate **128** with arylboronic acids as reported by Yoshida *et al*.[108]

In contrast to copper-mediated processes, methods utilising rhodium catalysis have been underdeveloped. In 2007, Murakami *et al*. described the stereoselective synthesis of α-allenols (e.g. **131**) by the S_N2'-type substitution of alkynyl epoxides (e.g. **130**) with arylboronic acids (e.g. **129**) (Scheme 65).[109]



Scheme 65: S_N2'-type rhodium-catalysed reaction of chiral alkynyl epoxide **130** with phenylboronic acid (**129**) as reported by Murakami *et al*.[109]

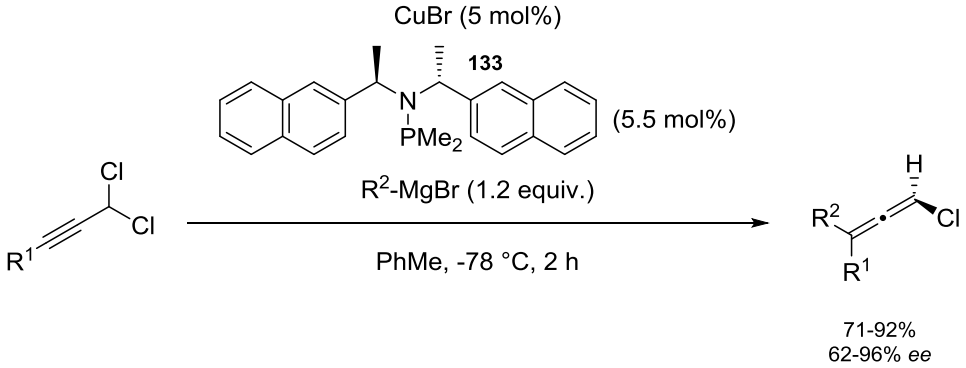
A significant drawback of this process, however, is the difficulty in generating these starting materials in a chiral fashion. To circumvent this issue, Ruchti and Carreira reported a rhodium-catalysed synthesis of allenes using propargylic benzoates and arylboronic acids in the presence of phosphoramidite ligand **132**, proceeding in moderate to excellent yields and high chirality transfer (Scheme 66).[110]



Scheme 66: S_N2'-type rhodium-catalysed reactions of chiral propargylic benzoates with arylboronic acids as reported by Ruchti and Carreira.[110]

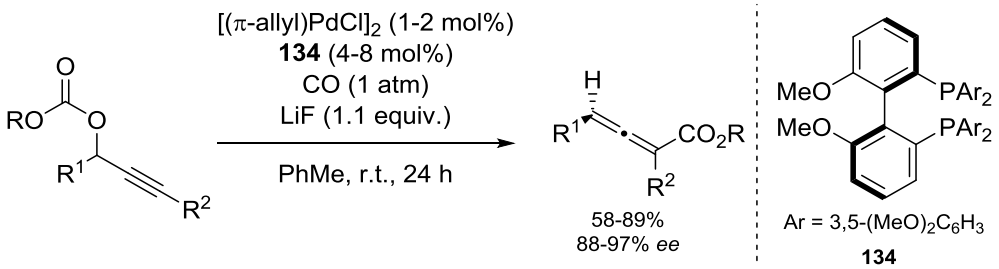
3.1.2. Reactions of racemic propargylic derivatives

In the presence of appropriate chiral ligands, it is possible to utilise racemic or achiral propargylic starting materials instead of enantiopure ones to synthesise chiral allenes. Alexakis *et al*. established that Grignard reagents in the presence of CuBr and phosphinamine ligand **133** react in an S_N2' fashion with achiral propargylic dichlorides, with good yields and moderate to high enantioselectivities, thus providing access to a variety of chiral chloroallenes that could be further derivatised to form various chiral trisubstituted allenes (Scheme 67).[111]



Scheme 67: Enantioselective S_N2' reactions of Grignard reagents with achiral propargylic dichlorides using copper catalysis and ligand **133** as reported by Alexakis *et al.*[111]

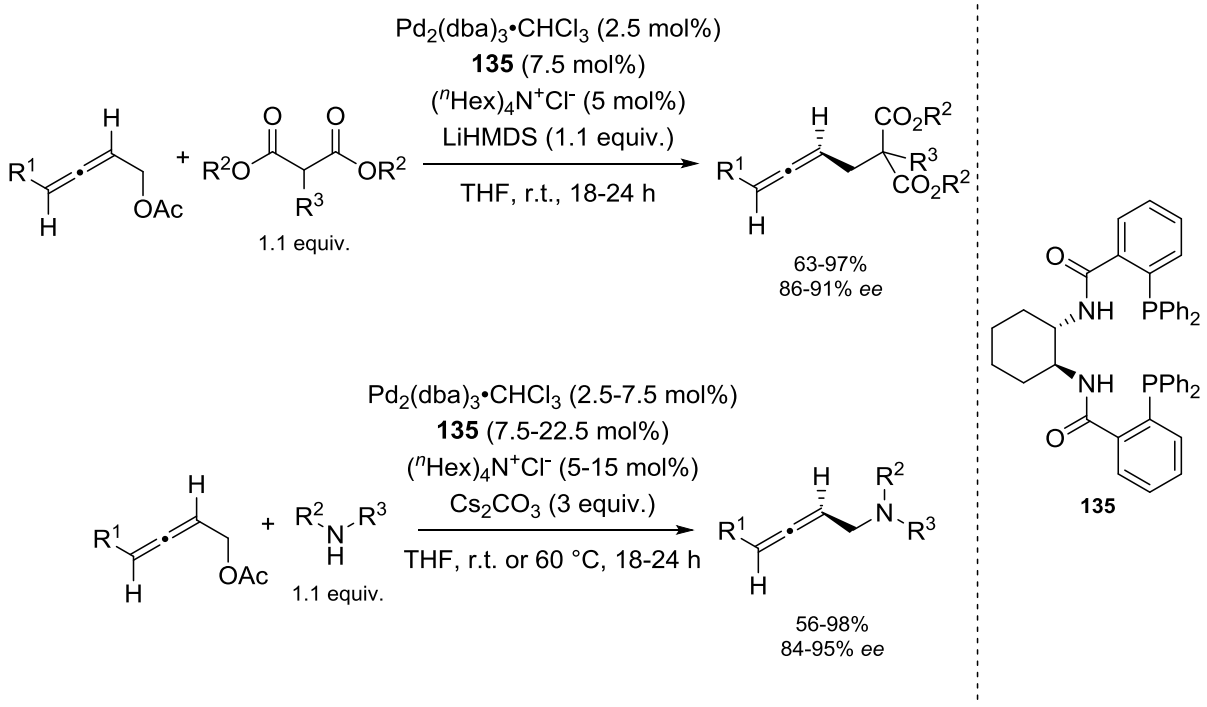
In addition, Ma *et al*. reported the dynamic kinetic asymmetric carbonylation of racemic propargylic carbonates, using allylpalladium(II) chloride dimer and diphosphine ligand **134**, providing allenyl esters in generally good yields and enantioselectivities (Scheme 68).[112]



Scheme 68: Dynamic kinetic asymmetric carbonylation of racemic propargylic carbonates using palladium catalysis and ligand **134** as reported by Ma *et al.*[112]

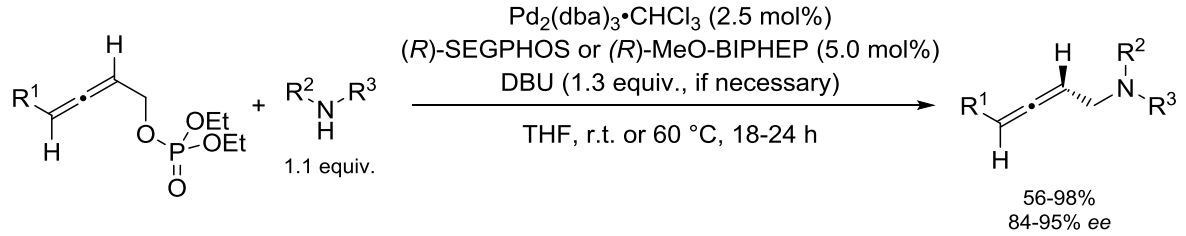
3.1.3. Asymmetric derivatisation of racemic allenes

With suitable leaving groups attached to the allene motif, it is possible to conduct enantioselective palladium-catalysed Tsuji-Trost alkylations and aminations to construct chiral allenes, as reported by Trost *et al.*[113] and Imada *et al.*[114] In the first case, diphosphine ligand **135** allowed the functionalisation of allenyl acetates using various malonates and amines as nucleophiles, providing generally good yields and high enantioselectivities (Scheme 69).



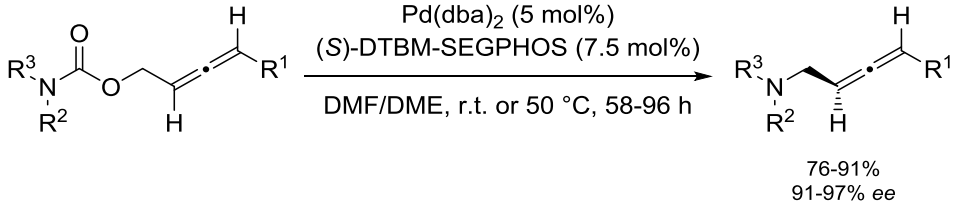
Scheme 69: Asymmetric Tsuji-Trost reactions of racemic allenic acetates with malonates and amines using diphosphine **135** as reported by Trost *et al.*[113]

In the second, allenyl phosphates are utilised instead and intercepted with amines, again leading to generally good yields and high enantioselectivities (Scheme 70).



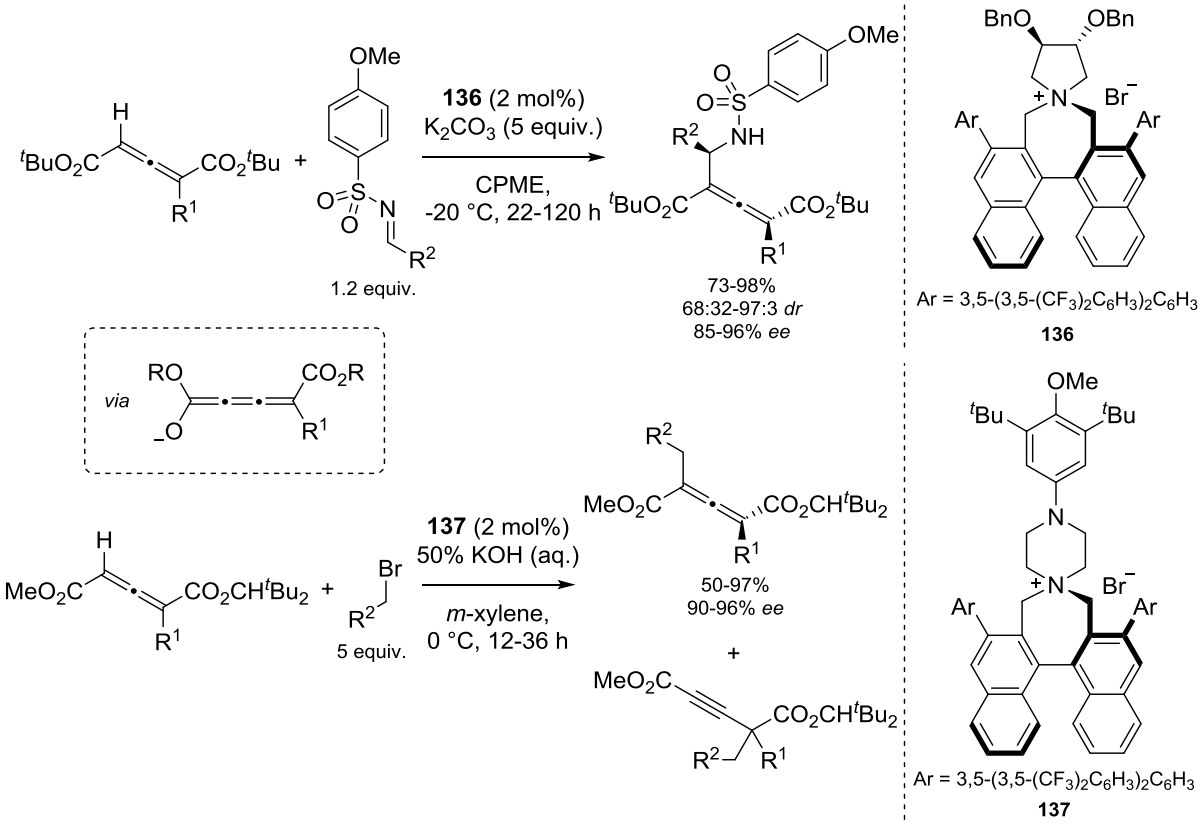
Scheme 70: Asymmetric Tsuji-Trost reactions of racemic allenic phosphates with amines as reported by Imada *et al.*[114]

A related approach presented by Wan and Ma uses allenyl carbamates instead; rather than reacting with an external nucleophile, palladium-catalysed decarboxylation of the allenyl carbamate generates the required nucleophile *in situ* (Scheme 71).[115] Significant drawbacks to this methodology include the difficulty in accessing the required starting materials and long reaction times.



Scheme 71: Asymmetric aminative decarboxylation of racemic allenyl carbamates as reported by Wan and Ma.[115]

In 2013, Maruoka *et al*. reported a different approach – by generating a cumulenoate nucleophile from racemic 1-alkylallene-1,3-dicarboxylates using an insoluble base and chiral ammonium salts **136** and **137** to act as phase-transfer catalysts, tetrasubstituted chiral allenes were synthesised by intercepting with imines and alkyl bromides, in high yields and enantioselectivities (Scheme 72).[116] For the alkylation however, occasionally a mixture of the desired allene product and an alkyne byproduct is observed, the latter resulting from reacting as an α-alkynyl enolate instead.

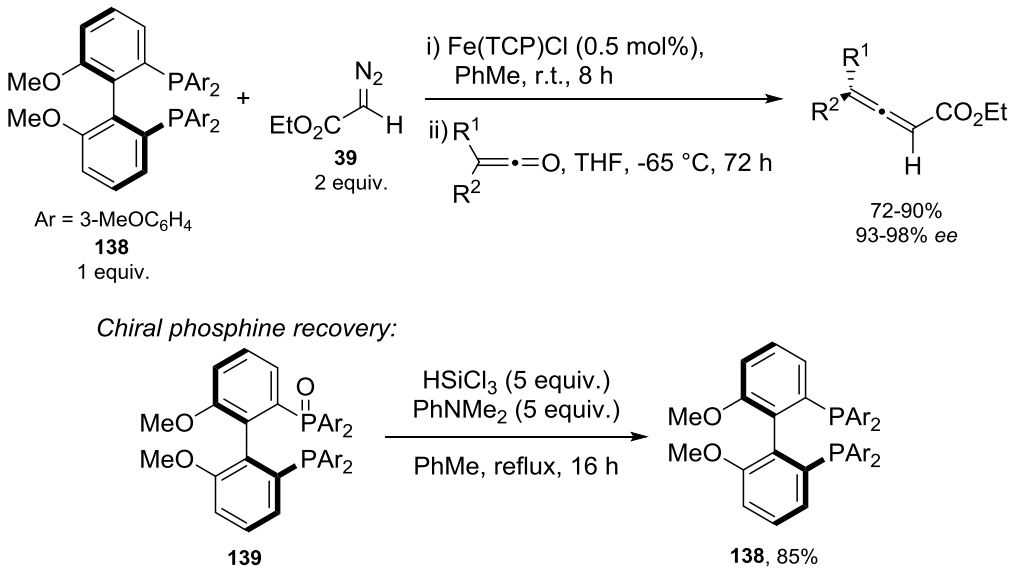


Scheme 72: Asymmetric phase-transfer catalysis using **136** or **137** for the synthesis of tetrasubstituted allenes by nucleophilic attack on imines and alkyl bromides as reported by Maruoka *et al.*[116]

3.1.4. Asymmetric coupling reactions of two simpler fragments

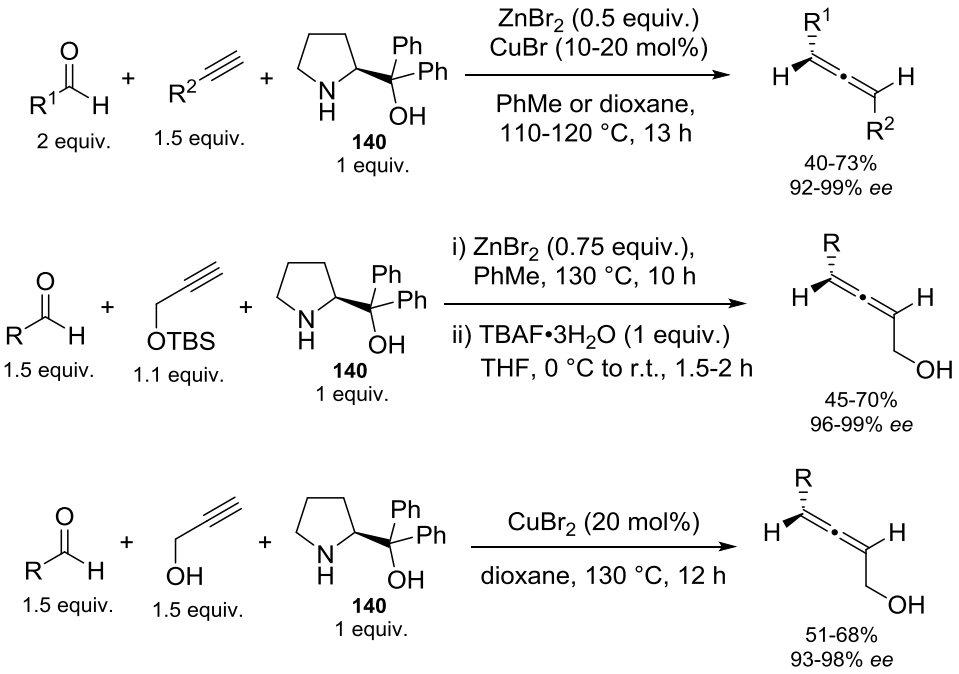
Asymmetric methods coupling two simpler fragments that result in formation of one of the allene C=C bonds can be split into two groups: ones utilising stoichiometric chiral mediators, and those that use catalytic quantities of a chiral ligand.

Tang *et al*. showed that ketenes can be transformed into ethyl allenoates by reacting with ethyl diazoacetate (**39**), using stoichiometric PPh_3 and Fe(TCP)Cl as the catalyst. By utilising stoichiometric chiral phosphine **138** instead, they were able to demonstrate efficient and highly enantioselective formation of the corresponding chiral ethyl allenoates (Scheme 73).[117] Although the use of stoichiometric quantities of chiral phosphine **138** is a major limitation, it was possible to recover chiral phosphine oxide **139**, regenerate phosphine **138** by reduction, then subsequently reuse the material in the enantioselective process.

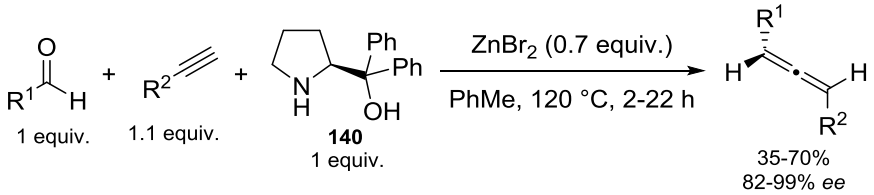


Scheme 73: Reaction of ketenes with ethyl diazoacetate (**39**) under iron catalysis using chiral phosphine mediator **138** as reported by Tang *et al.*[117]

Related to the racemic Crabbé route to generate allenes (coupling terminal alkynes with aldehydes), Ma *et al.*[118-120] (Scheme 74) and Periasamy *et al.*[121] (Scheme 75) have extensively investigated the use of chiral prolinol **140** to replace the dialkylamine reagent, proceeding under zinc(II) and/or copper(I) catalysis, or solely copper(II) catalysis.

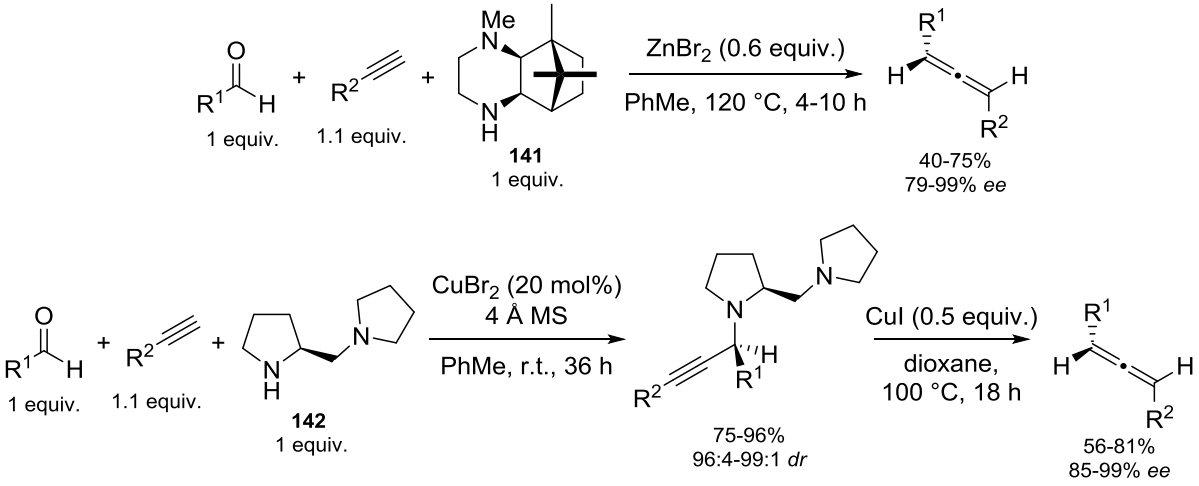


Scheme 74: Coupling reactions of terminal alkynes and aldehydes using prolinol **140** as reported by Ma *et al.*[118-120]



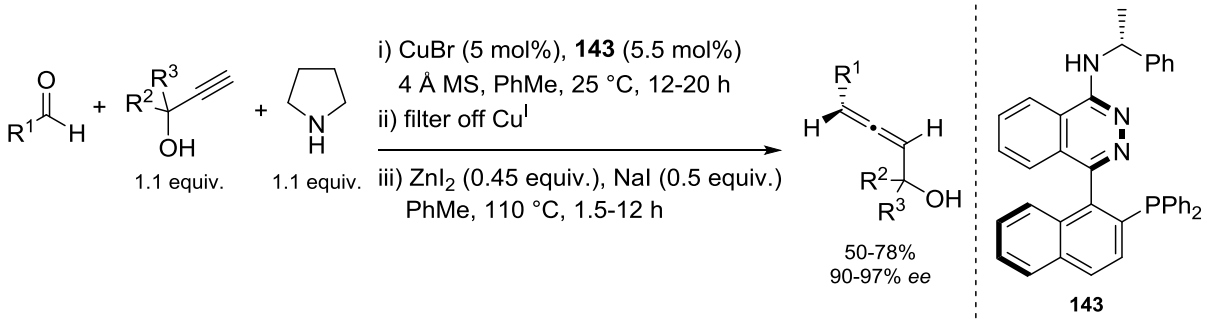
Scheme 75: Coupling reactions of terminal alkynes and aldehydes using prolinol **140** as reported by Periasamy *et al.*[121]

Alternative chiral amines investigated by Periasamy *et al*. such as chiral amines **141** and **142** have also shown utility (Scheme 76).[122,123] In most of these cases, good yields and high enantioselectivities were observed, though most of these processes require high catalyst or co-catalyst loadings.



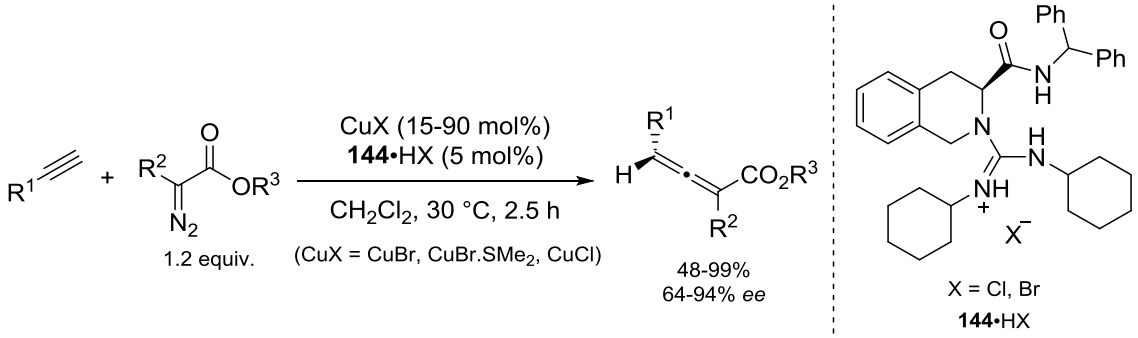
Scheme 76: Coupling reactions of terminal alkynes and aldehydes using chiral amines **141** and **142** as reported by Periasamy *et al.*[122,123]

A significant step was made in 2012 by Ma *et al*. to transform the original Crabbé method into a catalytic asymmetric process.[124] By using catalytic quantities of phosphine ligand **143** in the first CuBr-mediated step, filtration to remove copper(I) salts and then ZnI_2-mediated allene formation, it was possible to couple various propargyl alcohols with aldehydes, forming chiral disubstituted allenes (Scheme 77).



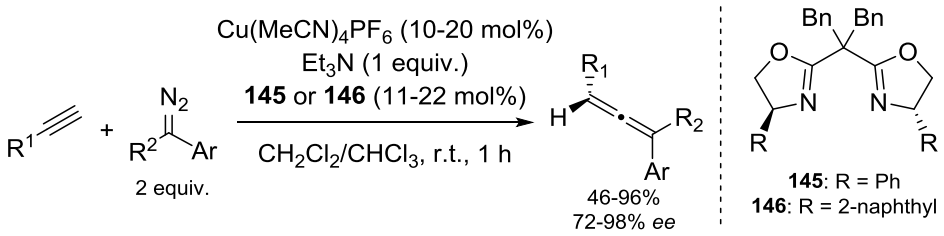
Scheme 77: Catalytic asymmetric coupling of propargyl alcohols with aldehydes using chiral phosphine ligand **143** as reported by Ma *et al.*[124]

Catalytic enantioselective couplings of diazo compounds and terminal alkynes have only been recently developed; in 2015, Feng *et al*. reported the coupling of stabilised α-diazoesters with terminal alkynes using chiral guanidium salts of **144** and copper(I) catalysis, providing a selection of both di- and trisubstituted allenoates in moderate to high yields with generally high enantioselectivities (Scheme 78).[125]



Scheme 78: Catalytic asymmetric coupling of terminal alkynes with stabilised α-diazoesters using chiral guanidium salts of **144** as reported by Feng *et al.*[125]

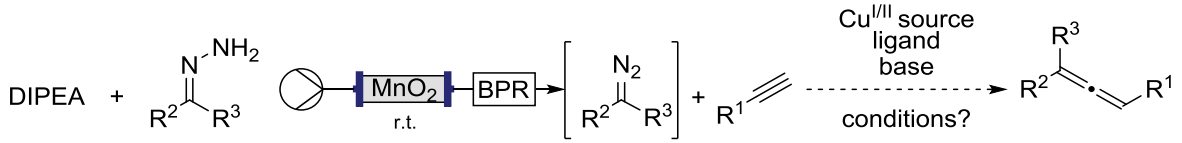
The first coupling of semi-stabilised aryl ketone-derived diazo compounds with terminal alkynes was described by Wang *et al*. in 2016, using $Cu(MeCN)_4PF_6$ and bidentate BOX ligands **145** or **146**, thus leading to trisubstituted allenes in generally good yields and high enantioselectivities (Scheme 79).[126]



Scheme 79: Catalytic asymmetric coupling of terminal alkynes with semi-stabilised aryl ketone-derived diazo compounds using BOX ligands **145** or **146** as reported by Wang *et al.*[126]

3.2. Aims of the project

It was envisaged that by exploiting the room temperature conditions used for the generation of semi-stabilised diazo compounds, it may be possible to conduct allene synthesis enantioselectively, in the presence of a suitable chiral ligand. At the outset of investigations into this potential process, the asymmetric coupling of semi-stabilised diazo compounds with terminal alkynes was unknown (the process described by Wang *et al.*[126] was published during our own investigations into this method). Therefore, the aims of this project centred on two goals: (a) to identify a suitable ligand for conducting the coupling process enantioselectively; and (b) to assess the reaction scope of this process (Scheme 80).



Scheme 80: Investigating the use of flow-generated semi-stabilised diazo compounds in asymmetric allene synthesis using a chiral ligand.

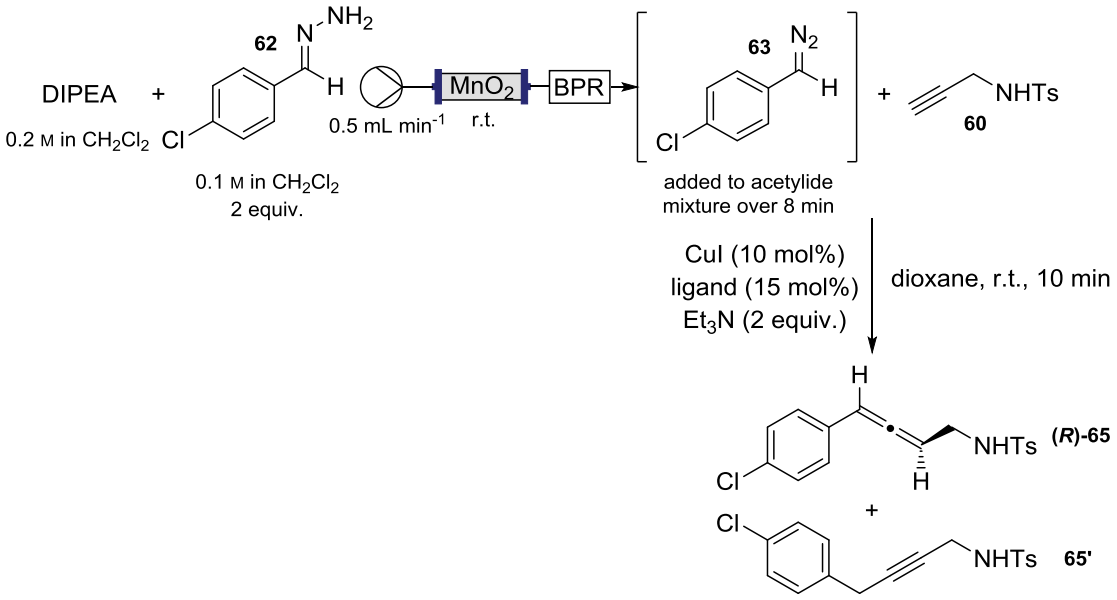
3.3. Results and discussion

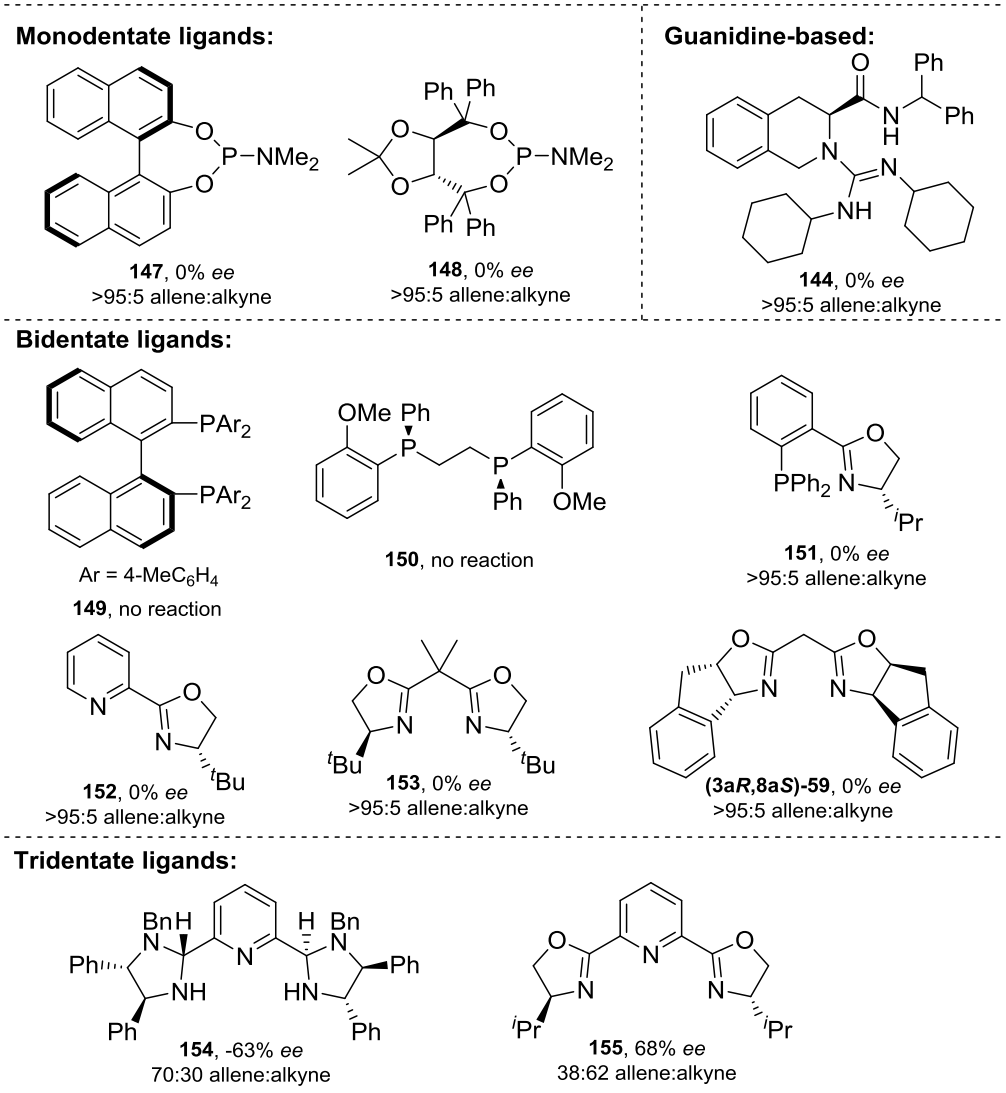
3.3.1. Initial screening for chiral ligands

Using our racemic allene synthesis as a starting point, we next focused on developing an asymmetric analogue of the diazo compound/terminal alkyne coupling. To begin, a selection of potential ligands were assessed (Scheme 81). Ligands were added (using 15 mol% of ligand) to copper(I) iodide to pre-form the required metal-ligand complex, then followed by base, terminal alkyne **60** and flow-generated diazo compound **63** in succession. Monodentate phosphine ligands **147** and **148** led to the reaction proceeding without any enantioselectivity, whereas the use of bidentate phosphine ligands **149** and **150** led to no conversion of the

alkyne starting material **60**. A mixed phosphine-imidazoline ligand **151** also provided good reactivity but no enantioselectivity, as did the pyridine-imidazoline ligand **152**. Interestingly, bidentate BOX ligands **153** and **(3a*R*,8a*S*)-59** were similarly ineffective for the coupling of this aldehyde-derived diazo compound. Use of the chiral guanidine-based catalyst **144** used by Feng *et al*.[125] also did not result in any enantioselectivity.

Whilst both monodentate and bidentate ligands did not result in useful enantioselectivity, tridentate ligands were found to be promising leads, with pyridinebis(imidazolidine) ligand **154** providing -63% *ee* and PyBOX ligand **155** providing 68% *ee*. In contrast to the racemic process where the allene product was formed exclusively, the alkyne cross-product **65′** was now found to be a byproduct of the reaction; a 70:30 allene:alkyne ratio was observed for ligand **154**, whereas a 38:62 allene:alkyne ratio was found for ligand **155**. For further ligand design studies, PyBOX ligand **155** was used as the initial lead ligand structure, due to the ease of access to enantiopure amino alcohols.



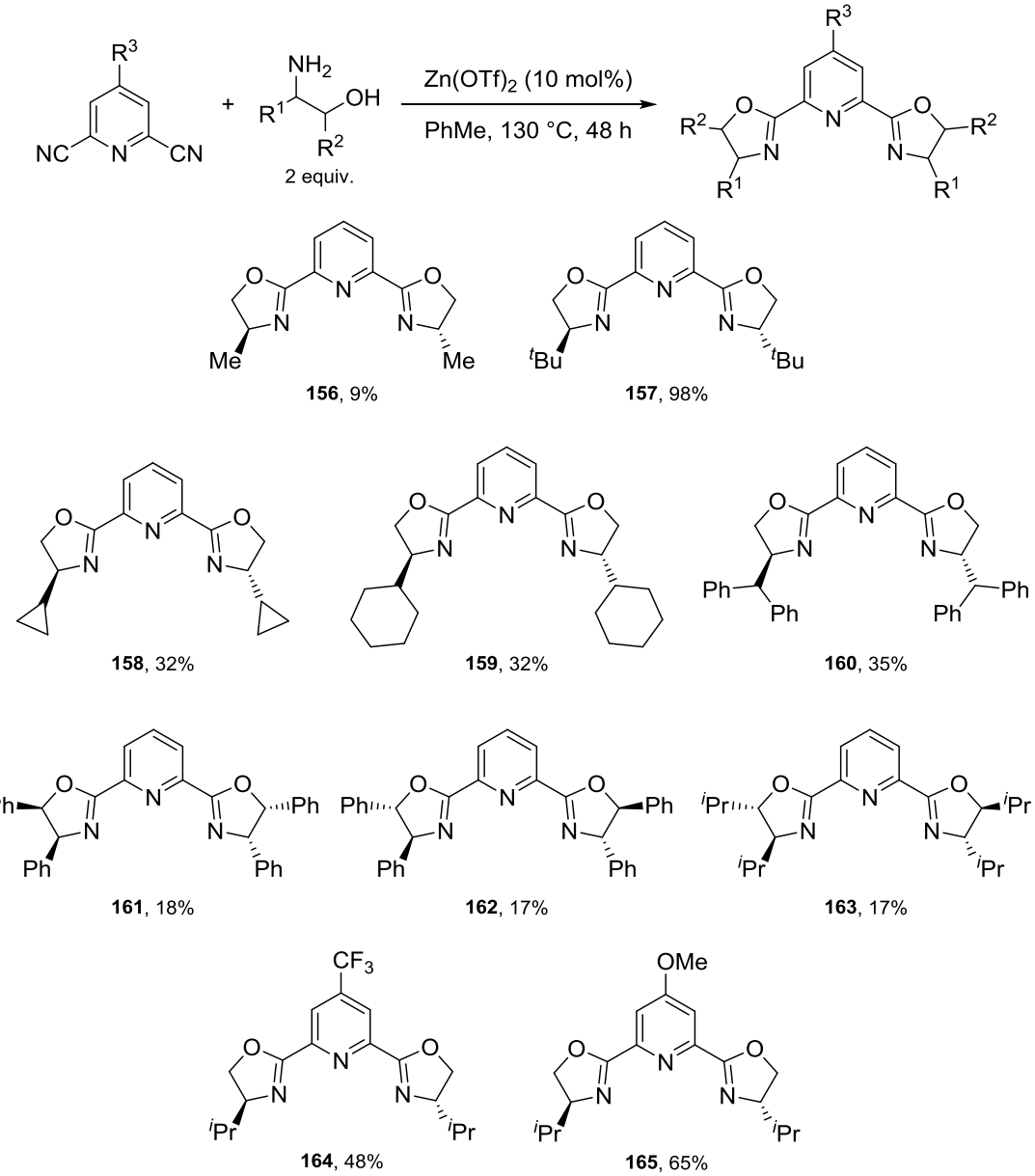


Reactions performed on 0.2 mmol scale with respect to terminal alkyne; all reactions proceeded in >95% conv.; allene:alkyne ratio determined by analysis of the crude ^{1}H NMR spectrum; *ee* determined by chiral HPLC.

Scheme 81: Initial ligand screening of various mono-, di- and tridentate ligands for asymmetric allene synthesis.

3.3.2. PyBOX ligands

Three different structural variations were assessed for developing new PyBOX ligands, which were synthesised from the condensation of pyridine-2,6-dicarbonitriles with amino alcohols using catalytic $Zn(OTf)_2$ (Scheme 82).[127] This involved varying the substituents on the oxadiazoline ring (R^1 and R^2) and the pyridine ring (R^3). Yields were highly variable (9-98%), however enough material was provided in the low-yielding cases for ligand testing and so the procedure was not further optimised.



Reactions performed on 1.0 mmol scale with respect to the pyridine-2,6-dicarbonitrile; yields stated are of isolated product.

Scheme 82: General route to PyBOX ligands *via* condensation of pyridine-2,6-dicarbonitriles with amino alcohols.

Structural variations in R^1 were relatively simple to explore due to the wide selection of commercially available amino alcohols. For these substituents, a switch from ^{i}Pr (**155**) to Me (**156**) resulted in a lower 45% *ee*, suggesting that the methyl group is not bulky enough to afford good enantioselectivity. However, an increase in steric bulk to ^{t}Bu (**157**) and Ph (**166**) also led to decreases in *ee* to 50% and 46% respectively (Figure 6).

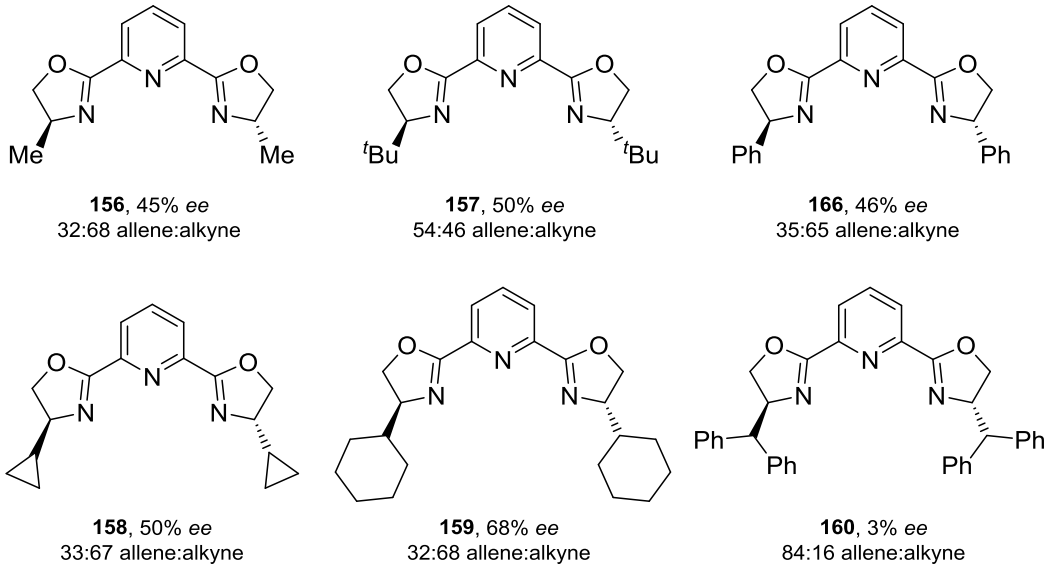
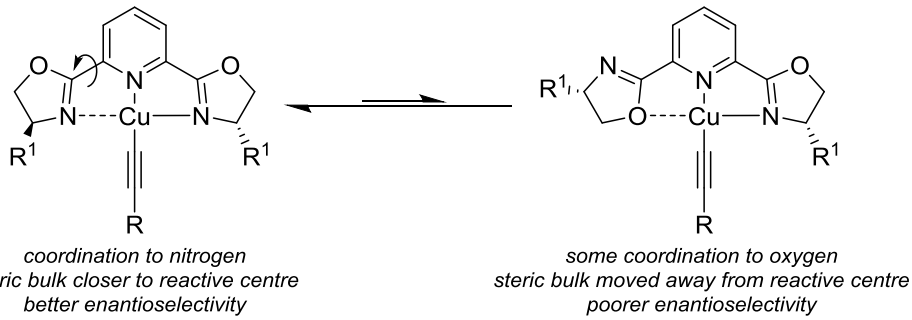


Figure 6: Effect of variation in R^1 of PyBOX ligands for asymmetric allene synthesis.

For these cases, it could be possible that with the larger tertiary alkyl and aryl groups, binding to the oxygen atom of the oxazoline unit becomes more preferable compared to the ^{i}Pr case, thus moving the steric bulk away from the reactive centre and thereby leading to poorer enantioselectivity (Scheme 83).

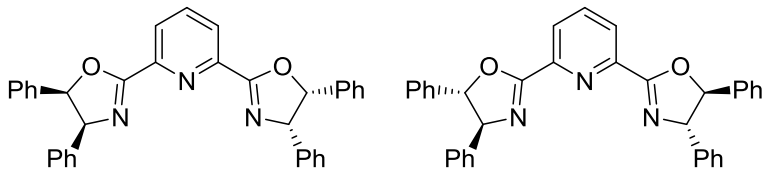


Scheme 83: Proposed rationale for poorer enantioselectivity with PyBOX ligands when steric bulk of R^1 is increased.

Since secondary alkyl groups appeared to be optimal for PyBOX ligands, three more substituents, cyclopropyl (**158**), cyclohexyl (**159**) and benzhydryl (**160**), were assessed for the

process. Both ligand **158** and **160** were found to be less efficient for enantioselectivity, at 50% and 3% *ee* respectively; for the former, the smaller bond angle in a cyclopropyl ring compared to an ^{i}Pr substituent leads to more compact steric bulk, whereas for the latter, the extreme bulk of the benzhydryl substituent could limit substrate binding. In the case of ligand **159**, enantioselectivity was the same as the ^{i}Pr case at 68% *ee*, but selectivity for the allene product was slightly poorer at a 32:68 allene:alkyne ratio (Figure 6). With these considerations, the ^{i}Pr group at R^1 was taken as optimal for further structural modifications on R^2 and R^3.

Variation of R^2 was not as facile to assess; both (1*R*,2*S*)-2-amino-1,2-diphenylethan-1-ol and (1*S*,2*S*)-2-amino-1,2-diphenylethan-1-ol are commercially available and allowed preparation of ligands **161** and **162**. When these were assessed for enantioselective allene formation, 55% and 80% *ee* were obtained respectively (Figure 7).

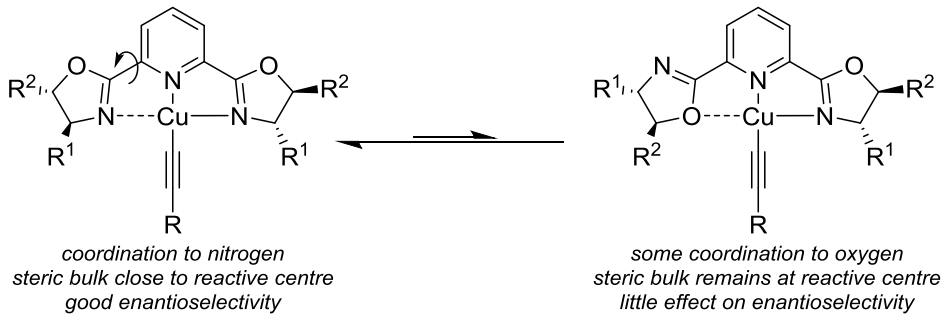


161, 55% *ee*
32:68 allene:alkyne

162, 80% *ee*
41:59 allene:alkyne

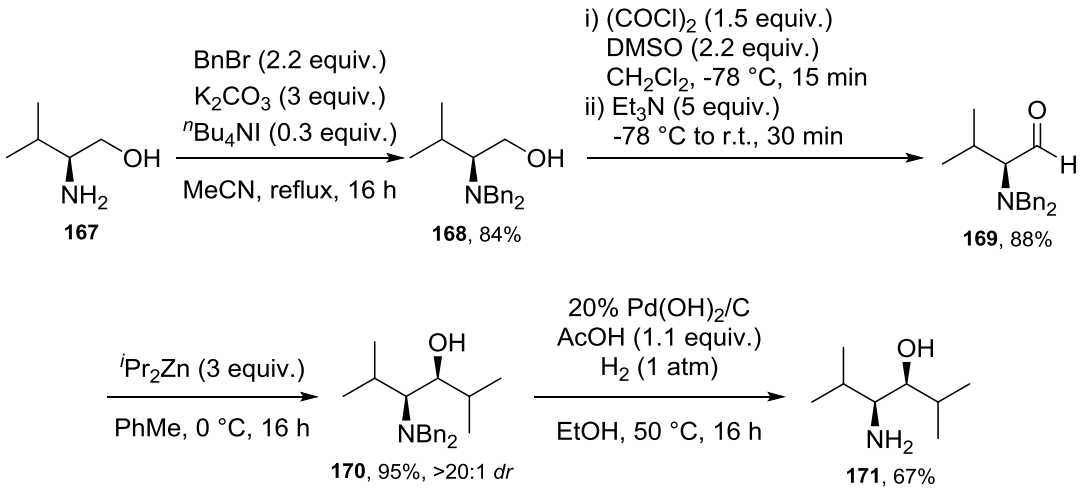
Figure 7: Effect of variation in R^2 of PyBOX ligands for asymmetric allene synthesis.

Of particular note, when compared to ligand **166** (R^1 = Ph, R^2 = H), ligand **162** (both Ph groups *anti* to each other) provided very good enantioselectivity. This appears to be consistent with the earlier hypothesis that for monosubstituted oxazoline PyBOX ligands, larger steric bulk can lead to preferable binding to the oxygen atom of an oxazoline unit; for the case of *anti*-disubstituted oxazoline PyBOX ligands such as **162**, coordination to the oxygen atom instead maintains steric bulk at the reactive centre and thus leads to high enantioselectivity (Scheme 84).



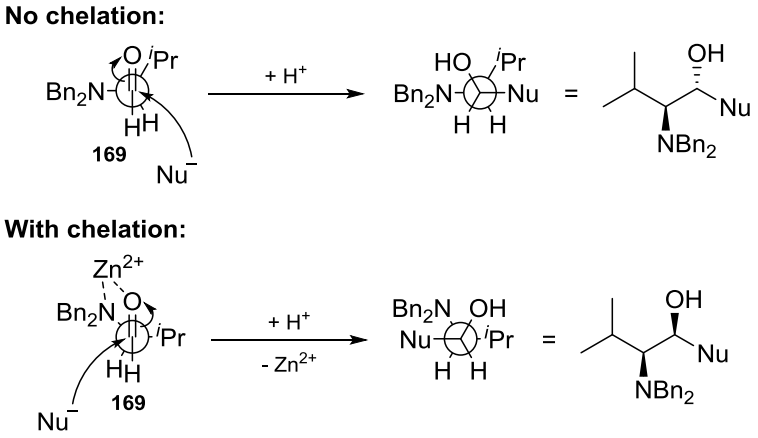
Scheme 84: Proposed rationale for higher enantioselectivity with PyBOX ligands when *anti*-disubstituted oxazolines are present.

With the ^{i}Pr group appearing to be optimal for monosubstituted oxazoline PyBOX ligands, investigation into the equivalent *anti*-disubstituted-^{i}Pr oxazoline PyBOX ligand **163** seemed prudent. The required amino alcohol **171** was synthesised in four steps from commercially available L-valinol (**167**), as depicted below (Scheme 85).



Scheme 85: Synthetic route to chiral amino alcohol **171**.

Benzyl protection of **167** provided **168** in 84% yield, which was then submitted to Swern oxidation to give the α-chiral aldehyde **169**. To obtain the correct diastereomer for the required *anti*-disubstituted oxazoline PyBOX ligand, attack on the α-chiral aldehyde must occur with *anti*-Felkin selectivity. Under normal Felkin-Anh control,[128] when the NBn_2 group is perpendicular to the aldehyde to provide the most reactive conformer, attack of a nucleophile past the smallest substituent (H atom) in the absence of chelation provides the *anti* amino alcohol.[129] In contrast, with chelation,[128] the NBn_2 group is now held in close proximity to the oxygen atom of the aldehyde and thus approach of the nucleophile is favoured from the opposite face (Scheme 86).[129]



Scheme 86: Nucleophilic attack on α-chiral aldehyde **169** under Felkin-Anh and chelation stereocontrol.

Hence, for the preparation of **170**, aldehyde **169** was treated with 3 equiv. of $^{i}Pr_2Zn$,[130] which provided protected amino alcohol **170** in 95% yield with very high diastereoselectivity. A final removal of the benzyl protecting groups by hydrogenation gave the unprotected amino alcohol **171** in 67% yield, which was submitted to PyBOX ligand formation as described earlier (Scheme 74) to provide ligand **163**. PyBOX ligand **163** was found to be slightly better than analogous diphenyl substituted analogue **162** at inducing enantioselectivity, providing allene **(*R*)-65** in 84% *ee*, though unfortunately the allene:alkyne ratio remained poor at 30:70 (Figure 8).

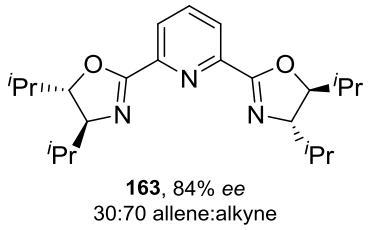
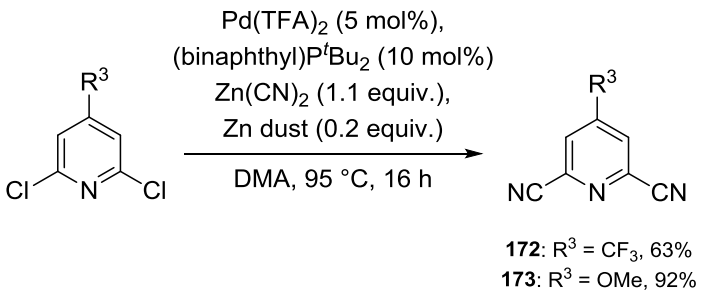


Figure 8: Performance of PyBOX ligand **163** for asymmetric allene synthesis.

For variation at R^3, an electron-withdrawing substituent (CF_3) and an electron-donating substituent (OMe) were picked to assess effects on enantioselectivity and allene:alkyne ratio. The required 4-substituted pyridine-2,6-dicarbonitriles were synthesised by palladium-catalysed cyanation of the corresponding 2,6-dichloropyridines,[131] providing **172** and **173** in 63% and 92% yields respectively (Scheme 87).



Scheme 87: Synthesis of 4-substituted pyridine-2,6-dicarbonitriles **172** and **173** by palladium-catalysed cyanation.

For asymmetric allene synthesis, the CF_3-substituted ligand **164** performed worse than the unsubstituted ligand **155**, at 47% *ee* compared to 68% *ee*, whereas the allene:alkyne ratio was slightly better at 48:52 (Figure 9). For this case, the CF_3-substituent seems to weaken binding of the ligand complex to the substrate, thus potentially leading to a greater extent of racemic allene coupling (leading to erosion of the enantioselectivity, but better allene:alkyne ratio). In contrast, the OMe-substituted ligand **165** provided 70% *ee* and a slightly poorer 36:64 allene:alkyne ratio, suggesting that the electron-rich nature of the pyridine ring is slightly enhancing complex binding.

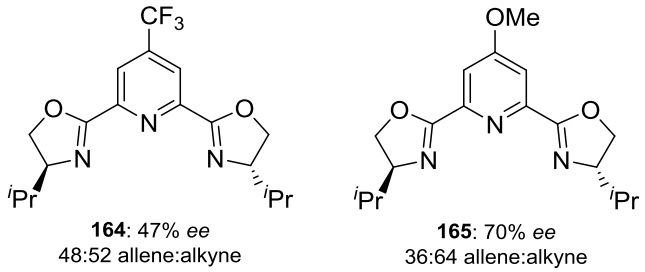
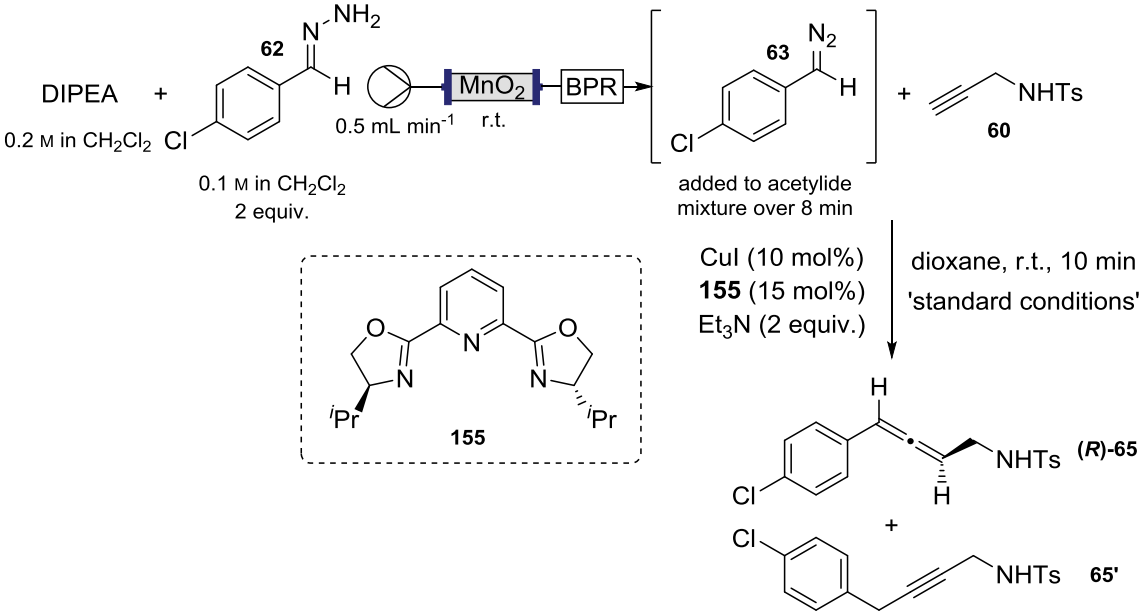


Figure 9: Effect of variation in R^3 of PyBOX ligands for asymmetric allene synthesis.

In all of the cases where significant enantioselectivities were observed for asymmetric allene formation under PyBOX/CuI catalysis, poor allene:alkyne ratios were also observed, usually furnishing the desired chiral allene **(*R*)-65** as the minor product. Conditions were therefore screened to assess whether any improvements in both enantioselectivity and the allene:alkyne ratio could be realised, using commercially available ligand **155**. Alternative solvents were found to be worse than the original dioxane/CH_2Cl_2 mixture: use of DMSO, MeCN and DMF led to complete loss in enantioselectivity, most likely due to these solvents outcompeting ligand **155** for binding to copper(I) (Table 4, entries 3, 6 and 8); whereas DME, CH_2Cl_2, THF and EtOAc provided 43-50% *ee* (Table 4, entries 2, 4, 5, and 7). Alternative metal catalysts, for example $Cu(MeCN)_4PF_6$, AuI and ZnI_2 led to no conversion to either allene **(*R*)-65** or

alkyne **65′** cross-coupled products (Table 4, entries 9-11). Other changes in the reaction conditions, for example at lower concentration (Table 4, entries 12), using protic additives such as $Et_3NH^+I^-$ or MeOH (Table 4, entries 13-14), or anhydrous conditions by addition of 4 Å molecular sieves (Table 4, entries 15) were all ineffective at promoting both good enantioselectivity and allene:alkyne ratio, leading to improvements in either aspect but not both. Alternative bases instead of Et_3N, were also found to be ineffective in improving enantioselectivity or allene:alkyne ratio, with TMEDA and quinine again appearing to outcompete ligand **155** for complexation to the copper catalyst (Table 4, entries 16-19).

Table 4: Screening alternative conditions for asymmetric allene coupling using PyBOX ligand **155**.



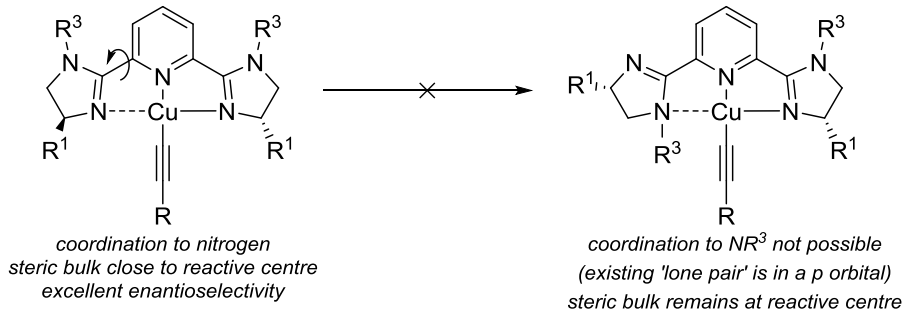
Entry	Deviation from standard conditions	Allene:alkyne ratio	*ee* / %
1	-	38:62	68
2	DME instead of dioxane	50:50	45
3	DMSO instead of dioxane	>95:5	0
4	CH_2Cl_2 instead of dioxane	48:52	43
5	THF instead of dioxane	42:58	48
6	MeCN instead of dioxane	81:19	0
7	EtOAc instead of dioxane	38:62	50
8	DMF instead of dioxane	81:19	0
9	$Cu(MeCN)_4PF_6$ instead of CuI	(no reaction)	
10	AuI instead of CuI	(no reaction)	
11	ZnI_2 instead of CuI	(no reaction)	
12	initial acetylide solution diluted 4-fold	48:52	40
13	2 equiv. $Et_3NH^+I^-$ added	88:12	7
14	2 equiv. MeOH added	40:60	64
15	4 Å MS added	38:62	66
16	DIPEA instead of Et_3N	38:62	62
17	TMEDA instead of Et_3N	>95:5	0
18	quinine instead of Et_3N	>95:5	8
19	Cs_2CO_3 instead of Et_3N	20:80	(n.d.)

Reactions performed on 0.2 mmol scale with respect to terminal alkyne; all reactions proceeded in >95% conv.; allene:alkyne ratio determined by analysis of the crude ^{1}H NMR spectrum; *ee* determined by chiral HPLC.

Since opportunities in structural variation of PyBOX ligands and changes in reaction conditions were becoming limited, particularly with little insight into improving allene:alkyne ratio independently of enantioselectivity, a change in focus to a different family of ligands was made, to pyridine(bisimidazoline) (PyBIM) ligands.

3.3.3. PyBIM ligands

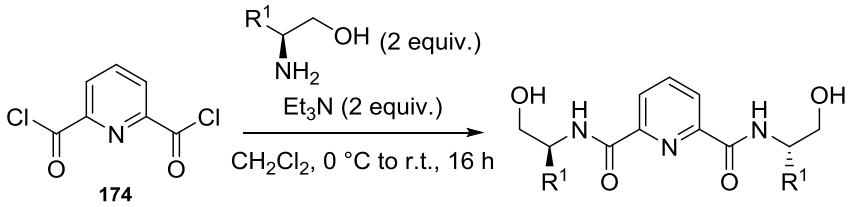
With the knowledge that the oxazoline units of PyBOX appear to act as ambidentate ligands, it was hypothesised that an appropriate approach would be to replace the oxazoline substituents with imidazolines. Unlike PyBOX ligands, the imidazoline substituents are not ambidentate, since they lack a suitably hybridised lone pair on the 1-position nitrogen atom to coordinate to metal ions (Scheme 88). Furthermore, functionalisation of this particular position offers opportunities in uniquely tuning steric and electronic parameters of the flanking imidazoline units, an aspect not amenable to exploration for PyBOX ligands.

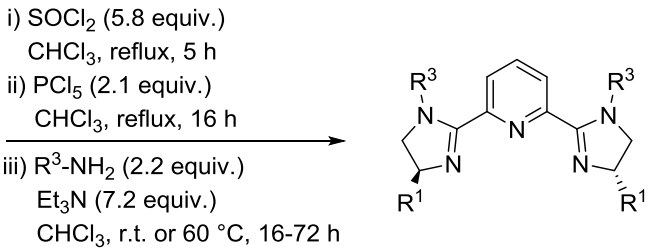


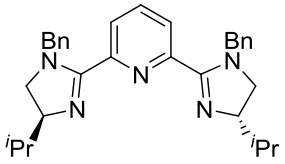
Scheme 88: Potential advantage of PyBIM ligands over PyBOX ligands to be investigated.

PyBIM ligands were generally synthesised in three steps as described by Ma and You,[132] starting from pyridine-2,6-dicarbonyl chloride (**174**). Reaction of **174** with amino alcohols provides the diamides (**175**, **176** and **177**), which were then chlorinated using $SOCl_2/PCl_5$ to form the imidoyl dichlorides. Subsequent cyclisation using anilines or alkyl amines generate the desired PyBIM ligands (Scheme 89).[‡] In general, cyclisation with unhindered, electron-rich anilines or amines (**178**, **179**, **181**, **183** and **184**) proceeded well, however lower yields were obtained in the cases of ligands **180** or **182** where a bulky aniline/amine was used. The use of electron-poor anilines required longer reaction times and/or higher temperature to cyclise (**185-191**). Again, since enough material was obtained for ligand testing, no further attempt was made to optimise yields.

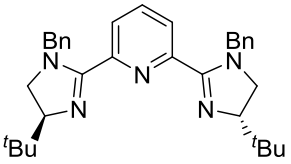
[‡] This work was conducted in collaboration with Timo von Keutz and Szabolcs Makai.



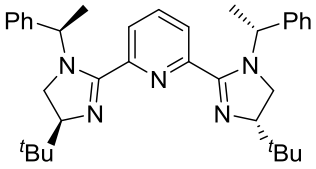




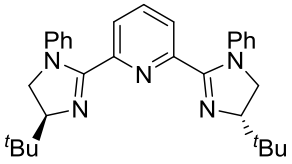
178, 47%



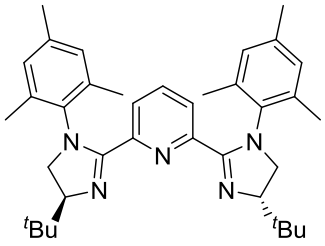
179, 39%



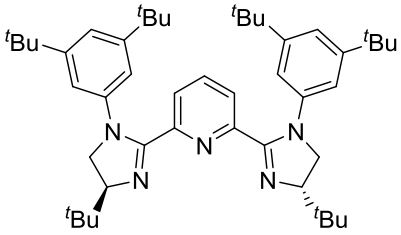
180, 10%



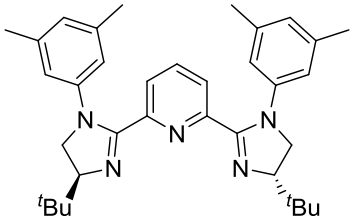
181, 89%



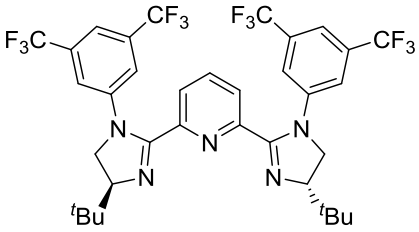
182, 24%



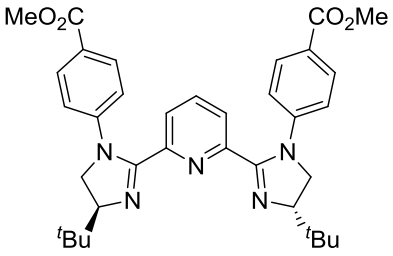
183, 57%



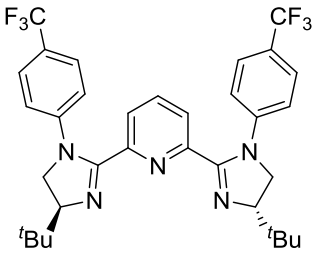
184, 77%



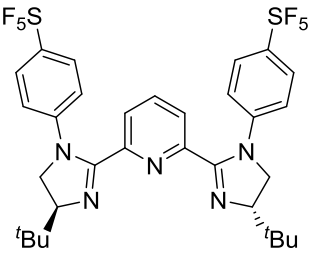
185, 43%



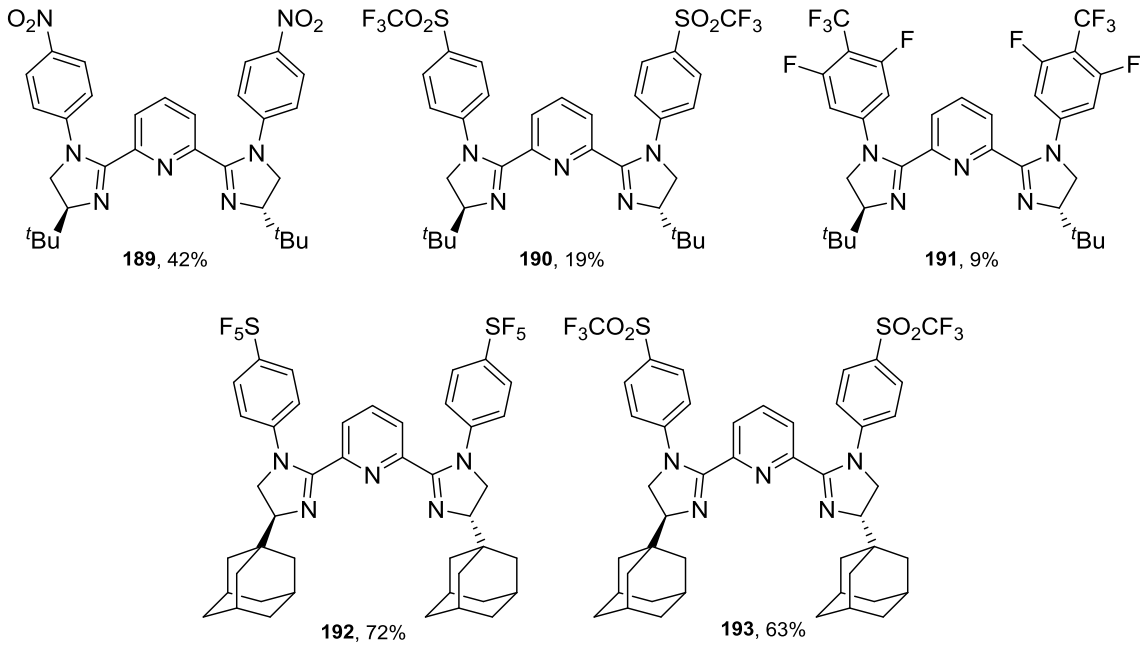
186, 44%



187, 70%



188, 57%



Reactions performed on 0.5 mmol scale with respect to the respective amides; yields stated are of isolated product from the chlorination/cyclisation sequence.

Scheme 89: General route to PyBIM ligands *via* amide formation, chlorination and cyclisation.

For these ligands, four different structural variations were investigated at R^1, R^2, R^3 and R^4 (Figure 10).

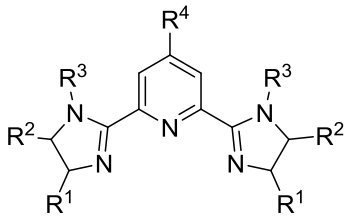


Figure 10: Structural variations in PyBIM ligands to be investigated for asymmetric induction.

For variation of R^1, an ^{i}Pr substituent for ligand **178** (with Bn as the substituent at R^3) provided allene **(*R*)-65** in similar enantioselectivity to the similar PyBOX ligand **155**, but with a better 70:30 allene:alkyne ratio (Figure 11). A change from ^{i}Pr (**178**) to ^{t}Bu (**179**) gave an increase in *ee* to 86% whilst allene:alkyne selectivity fell to 47:53. This effect of increasing steric bulk for PyBIM ligands sharply contrasts with the trend observed with PyBOX ligands, consistent with the imidazoline moieties being monodentate rather than ambidentate like the oxazolines.

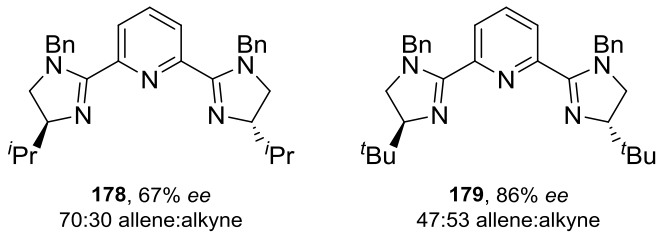
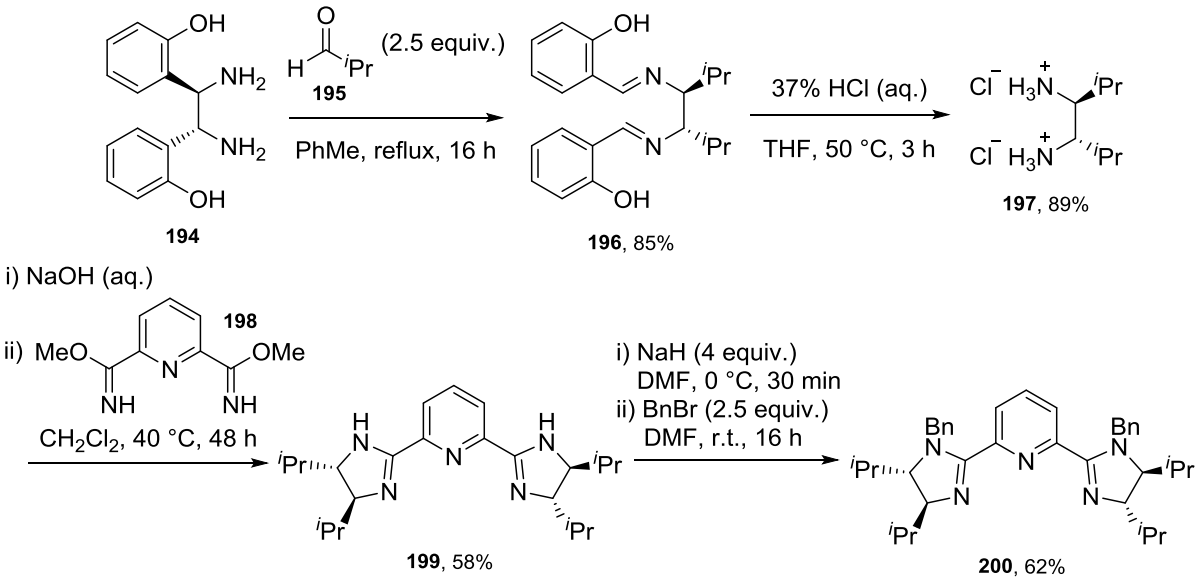


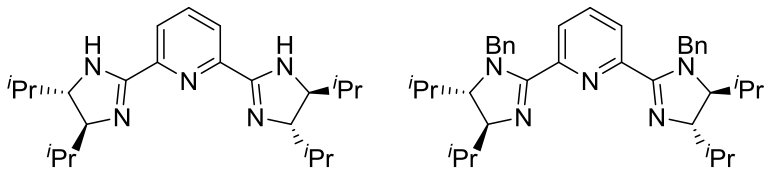
Figure 11: Effect of variation in R^1 of PyBIM ligands for asymmetric allene synthesis.

Substituents at R^2 were difficult to vary extensively, though it was possible to access PyBIM ligands analogous to PyBOX ligand **163**. For these two ligands, a different synthetic approach was taken as outlined below, due to the lengthy route to accessing amino alcohol **171** (Scheme 77). As reported by Chin *et al*.,[133] starting from the commercially available 'Mother diamine' **194**, condensation with isobutyraldehyde (**195**) and a subsequent diaza-Cope rearrangement afforded **196** in 85% yield; hydrolysis of this intermediate provided 89% of chiral diamine dihydrochloride **197**. Condensation of diamine **197** with imidate **198** (synthesised by methanolysis of 2,6-pyridinedicarbonitrile) gave ligand **199** in 58% yield, and alkylation of **199** with BnBr provided ligand **200** in 62% yield (Scheme 90).



Scheme 90: Synthetic route to PyBIM ligands **199** and **200**.

Ligand **199** performed marginally better for enantioselectivity than the monosubstituted imidazoline ligand **178**, whereas for ligand **200**, *ee* sharply decreased to 19% (Figure 12). Since simultaneous substitution at R^1, R^2 and R^3 appeared to be detrimental to asymmetric induction, investigations into variation of R^2 were halted and subsequent ligand designs were kept monosubstituted on the imidazoline moieties (i.e. R^2 = H).



199, 71% *ee*
64:36 allene:alkyne

200, 19% *ee*
>95:5 allene:alkyne

Figure 12: Effect of variation in R^2 of PyBIM ligands for asymmetric allene synthesis.

For variation of R^3 (using R^1 = ^{t}Bu), a change from Bn to a (*R*)-1-phenylethyl substituent for ligand **180** led to a decrease in *ee* to 25%, whereas a change to Ph for ligand **181** pleasingly increased the enantioselectivity to 96% *ee*, with a 32:68 allene:alkyne ratio (Figure 13). An attempt to increase steric bulk of R^3 using di-*ortho*-substituted anilines, such as for ligand **182**, only led to eroded enantioselectivity. Use of di-*meta*-substituted anilines reduced enantioselectivity slightly compared to ligand **181**, with 88-89% *ee* for all three ligands **183**, **184** and **185**. Promisingly, it appeared that variation of the electronics of R^3 was important for adjusting the allene:alkyne ratio independently of enantioselectivity, with more electron-withdrawing aromatic rings leading to higher allene:alkyne ratios, in particular with **185** providing an allene:alkyne ratio of 68:32. Further investigation into *para*-substituted anilines revealed that enantioselectivity was maintained at high levels between 96-97% *ee* for ligands **186**, **187** and **188**, with allene:alkyne ratios becoming better with increased electron deficiency, to a maximum of 62:38 for ligand **188**. Further decreases in electron density by using a nitro (**189**) or triflyl (**190**) substituent were detrimental, probably due to weakening binding to the copper(I) centre. Installation of a 3,5-difluoro-4-trifluoromethylaniline analogue (**191**) was detrimental to enantioselectivity, so the 4-SF_5 substituent was picked for the final structural variations.

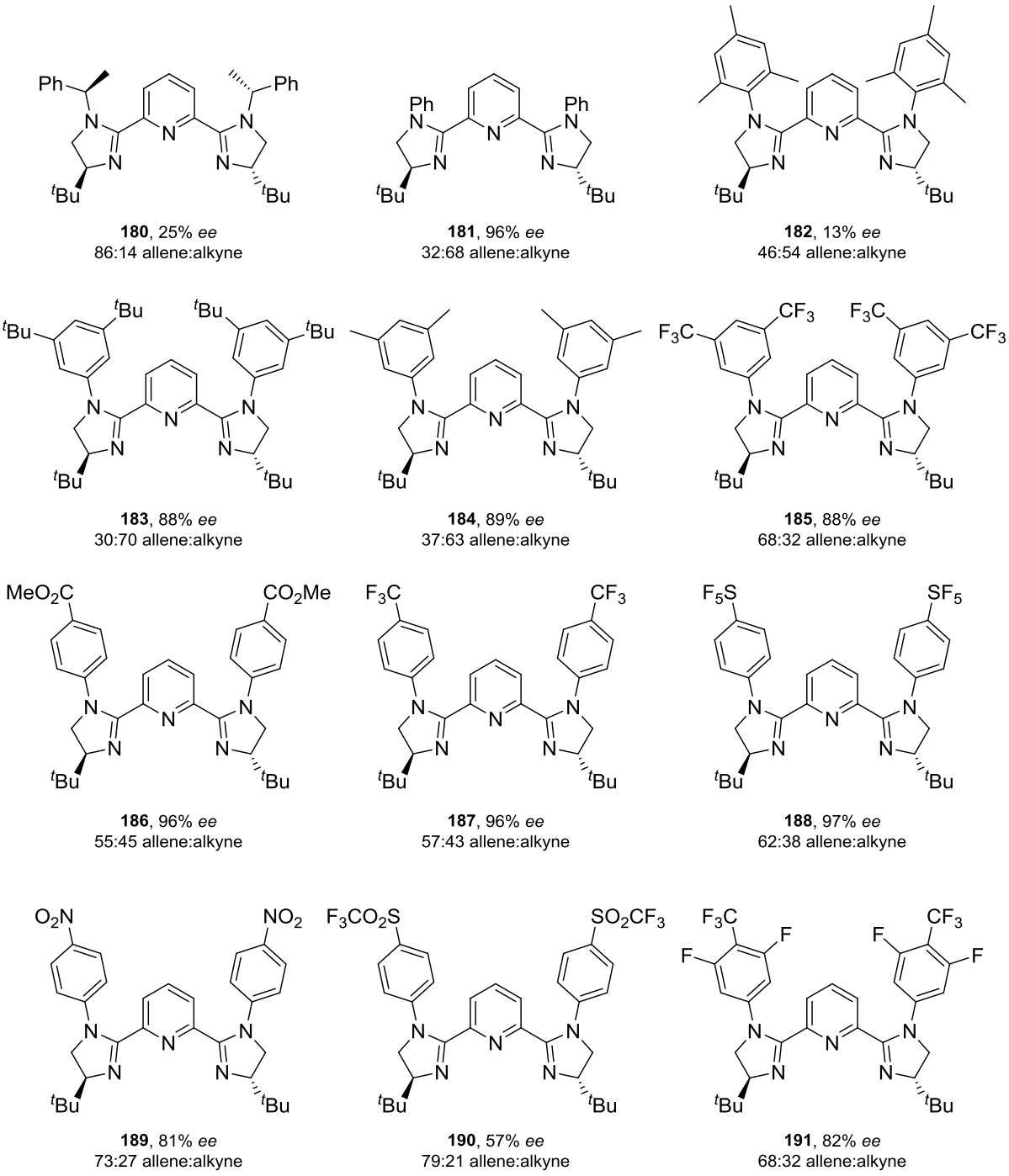
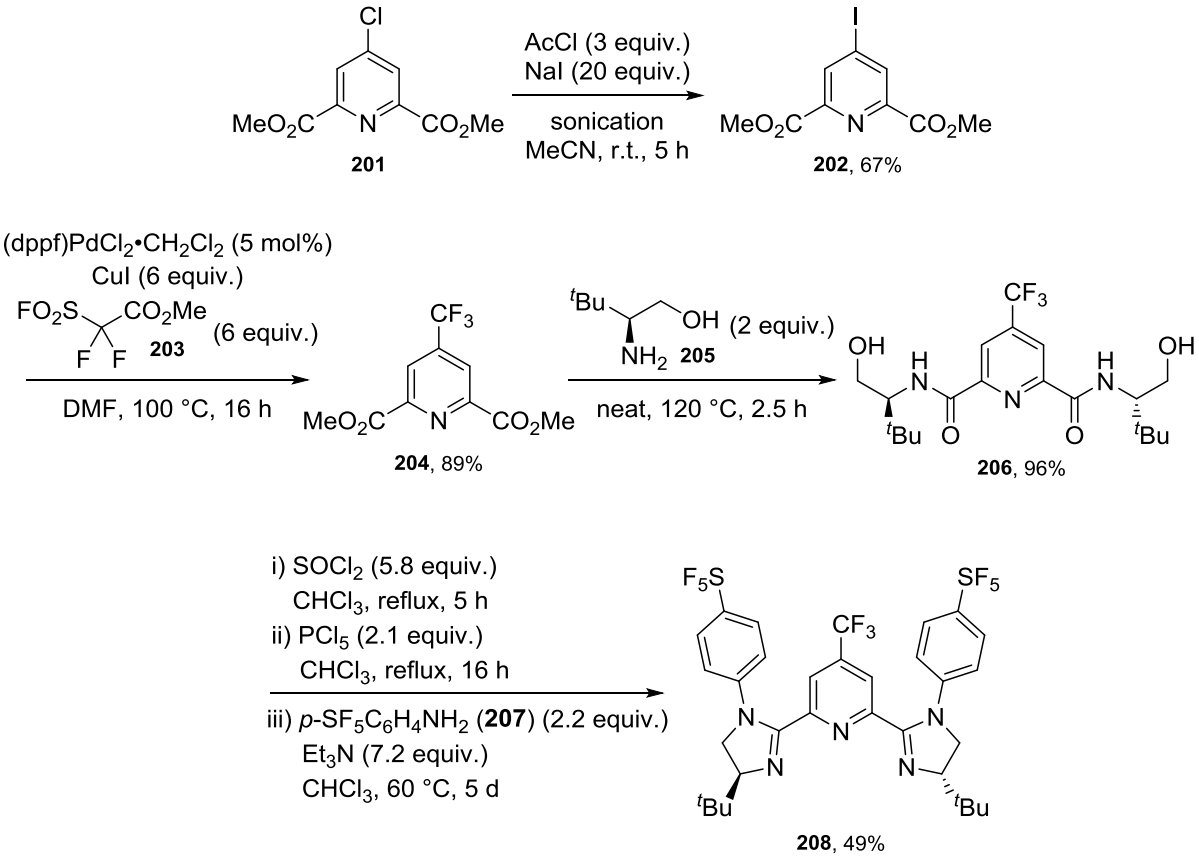


Figure 13: Effect of variation in R^3 of PyBIM ligands for asymmetric allene synthesis.

As enantioselectivities were already high for ligand **188**, a potential line of approach was to increase electron deficiency in the pyridine ring, in an attempt to provide better allene:alkyne selectivities. Ligand **208**, with a CF_3 substituent for R^4 to assess the impact of this structural change, was synthesised using the approach below (Scheme 91).



Scheme 91: Synthetic route to 4-CF_3 substituted ligand **208**.

Commercially available substituted pyridine **201** was iodinated to provide **202**, then submitted to palladium-catalysed trifluoromethylation using **203** to provide diester **204**. Reaction with L-*tert*-leucinol (**205**) as described by Parsons and Johnson[134] provided diamide **206**, which was then chlorinated and cyclised with aniline **207** as described previously for PyBIM synthesis to provide ligand **208** in 49% yield. Unfortunately, whilst ligand **208** did provide better allene:alkyne selectivity at 78:22, *ee* was markedly decreased to 63% (Figure 14).

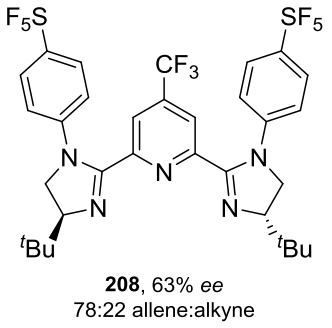
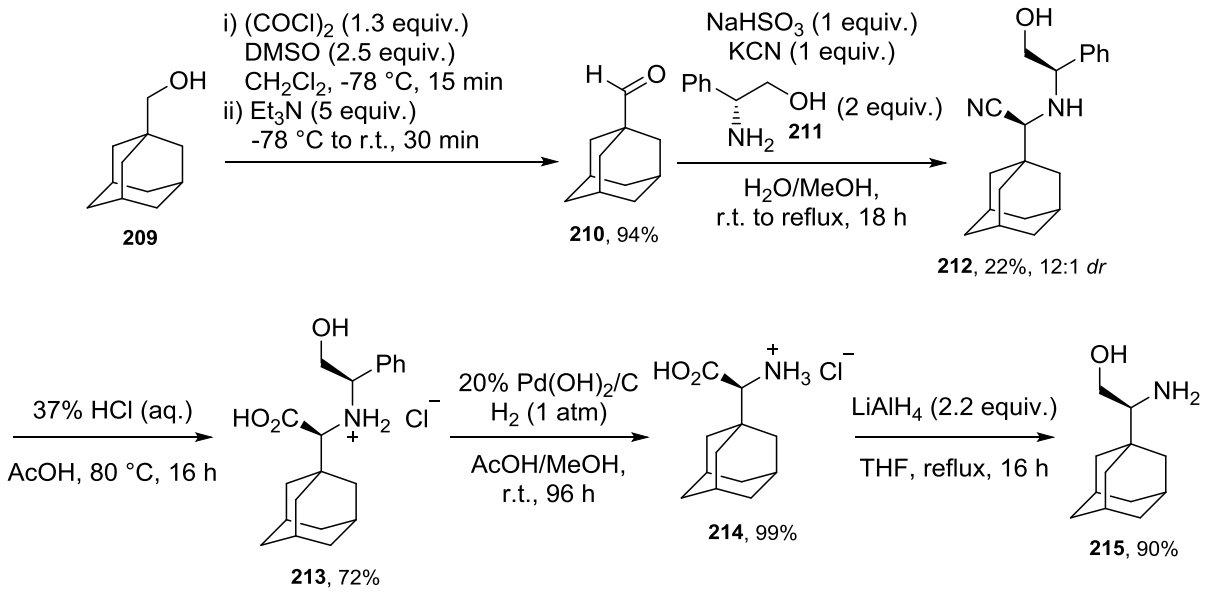


Figure 14: Performance of PyBIM ligand **208** for asymmetric allene synthesis.

To conclude ligand optimisation, it was decided to return to substituent R^1 and replace ^{t}Bu with a bulkier adamantyl substituent. Chiral amino alcohol **215** was obtained in five steps from 1-adamantanemethanol (**209**), as shown below using the route described by Hamann *et al*. (Scheme 92).[135] Swern oxidation gave aldehyde **210** in 94% yield, which was then subjected to a Strecker reaction using (*R*)-phenylglycinol (**211**) as a chiral auxiliary, providing **212** in 22% yield with good diastereoselectivity. Hydrolysis of the nitrile group gave 72% of **213**, then submitted to hydrogenation to give chiral amino acid **214** in quantitative yield. Finally, reduction using $LiAlH_4$ gave the desired amino alcohol **215** in 90% yield, which was smoothly utilised for PyBIM synthesis to provide ligands **192** and **193** (Scheme 89).



Scheme 92: Synthetic route to chiral adamantyl-substituted amino alcohol **215**.

Whilst these ligands had relatively high enantioselectivities at 91% and 93% *ee* respectively, these enantioselectivities were poorer than the 97% *ee* obtained for ligand **188**, and allene:alkyne ratios also similar (Figure 15).

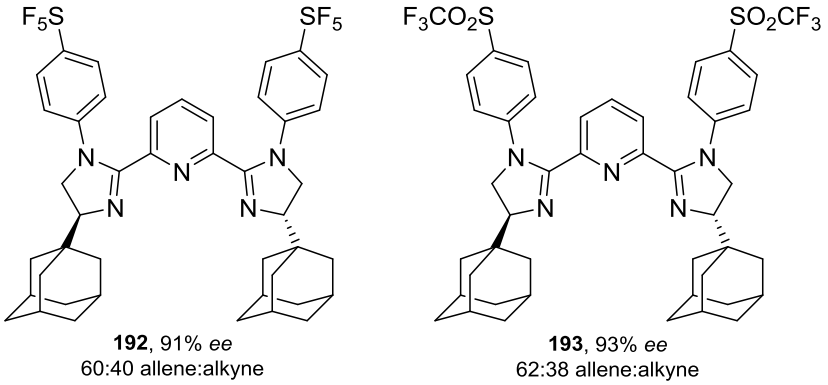
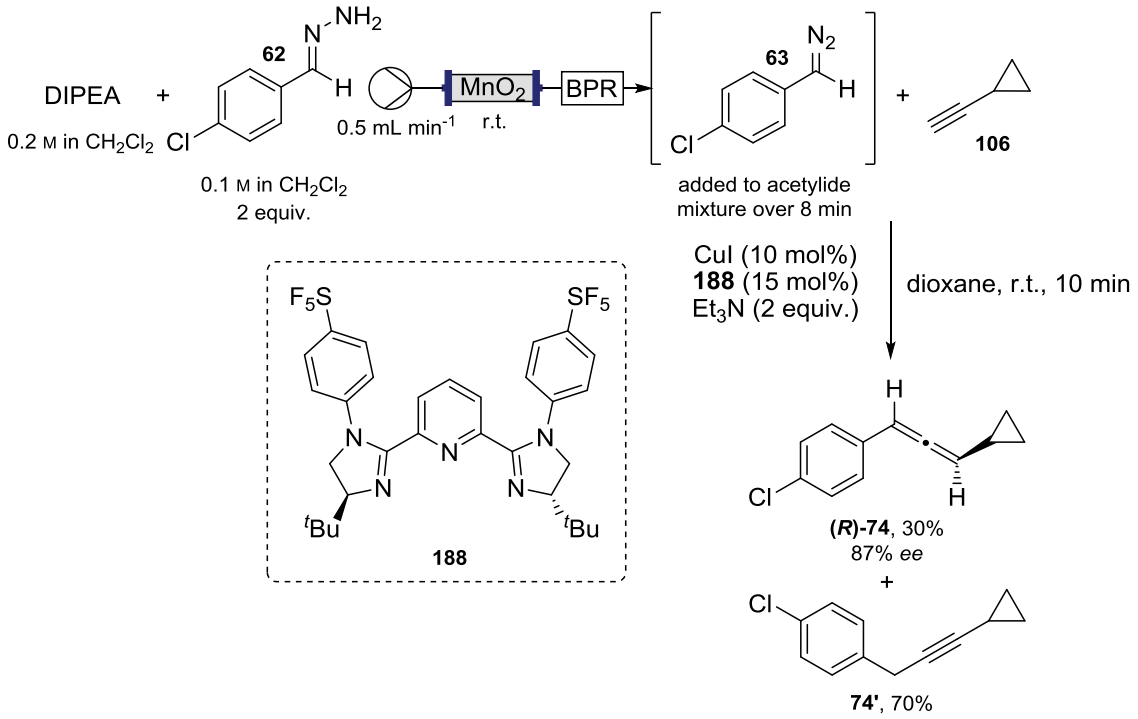


Figure 15: Performance of adamantyl-substituted PyBIM ligands **192** and **193** for asymmetric allene synthesis.

Ligand **188**, with 97% *ee* and 62:38 allene:alkyne selectivity, was therefore chosen for investigation into the scope of the asymmetric allene coupling.

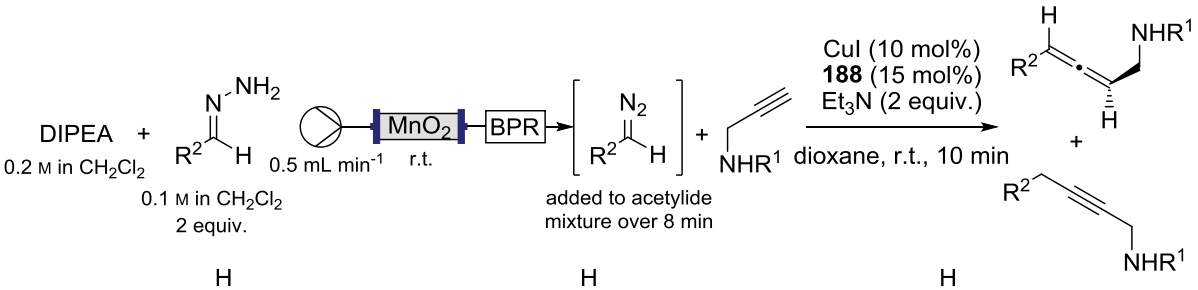
3.3.4. Reaction scope

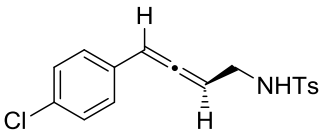
An early attempt to generalise the scope using cyclopropylacetylene (**106**) provided good enantioselectivity (87% *ee*) of allene **(*R*)-74**. However, only 30% of **106** was converted to the allene, with the remainder being converted to alkyne cross-coupled product **74′**, i.e. much poorer than the results during ligand design with substrate **60** (Scheme 93). At this point it was postulated that the N-H of the sulfonamide group could play an important role in the reaction mechanism, possibly acting as an internal proton source to favour formation of the allene cross-coupled product (Section 3.3.6).



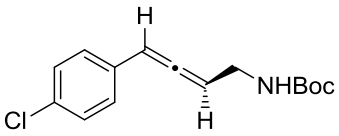
Scheme 93: Asymmetric allene coupling of diazo compound **63** with cyclopropylacetylene (**106**).

Various substrates with suitably acidic N-H protons (e.g. sulfonamides, carbamates, amides) were consequently used for asymmetric allene coupling, providing moderate yields of the chiral allenes **(*R*)-65**, **(*R*)-77** and **216**, with the remainder of the starting material being converted to the corresponding alkyne cross-coupled products. A myriad of functional groups installed onto the propargylamine were compatible with the reaction conditions, including trifluoromethyl (**217** and **236**), ketones (**218**), aldehydes (**219**), epoxides (**220**), unprotected alcohols (**223**), cyclopropanes and cyclopentanes (**224** and **225**), esters (**226** and **235**), internal and external olefins (**232-234**), all with high enantioselectivities and occurring very rapidly, reaching full completion 10 min after addition of the diazo compound. Heterocycles including thiophenes (**221**) and furans (**222**) were also tolerated, although for the former the reaction time was slightly longer at 20 min (probably due to coordination of thiophene to the copper(I)/ligand complex, thus hindering binding of alkynes to the catalyst). Both electron-donating (**229** and **235**) and electron-withdrawing (**230** and **232**) substituents for the semi-stabilised aryl diazo compound were tolerated, along with various halide substituents (**227**, **228**, **231**) again in moderate yields and high enantioselectivities. For more electron-withdrawing substituents on the aryl diazo compound, slightly poorer allene:alkyne ratios were observed, such as for allenes **228**, **230**, **232** and **234** (Scheme 94).

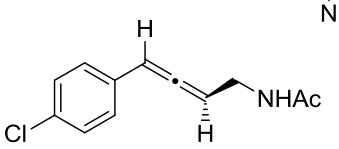




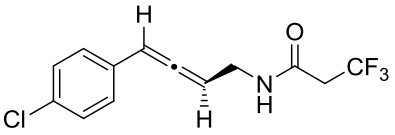
(*R*)-65, 51% (+28%)
97% *ee*



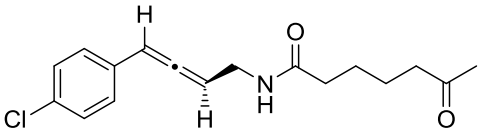
(*R*)-77, 49% (+35%)
93% *ee*



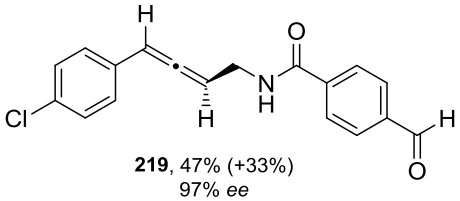
216, 47% (+32%)
94% *ee*



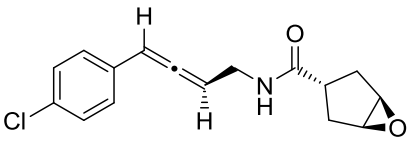
217, 52% (+26%)
91% *ee*



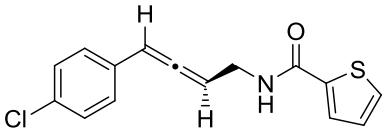
218, 49% (+38%)
96% *ee*



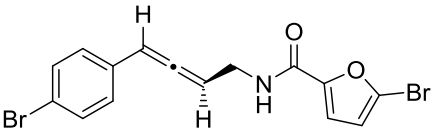
219, 47% (+33%)
97% *ee*



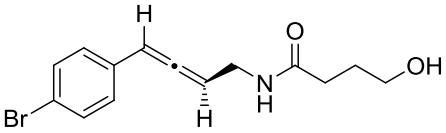
220, 55% (+37%)
95% *ee*



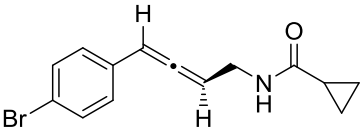
221, 53%* (+38%)
95% *ee*



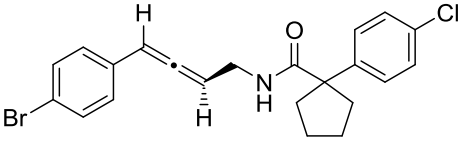
222, 53% (+39%)
96% *ee*



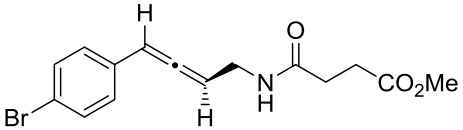
223, 49% (+37%)
91% *ee*



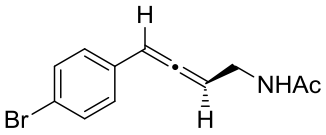
224, 51% (+35%)
95% *ee*



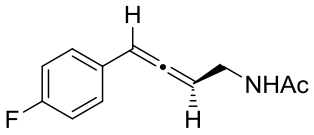
225, 47% (+29%)
95% *ee*



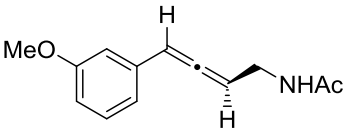
226, 43% (+37%)
91% *ee*



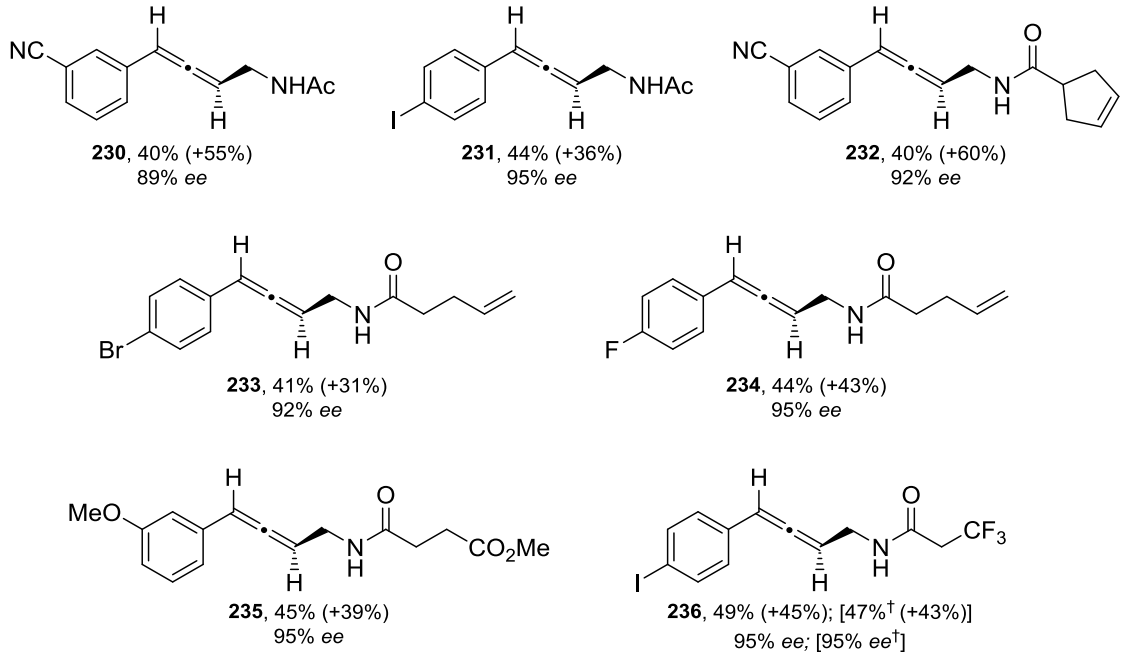
227, 51% (+38%)
96% *ee*



228, 45% (+35%)
91% *ee*



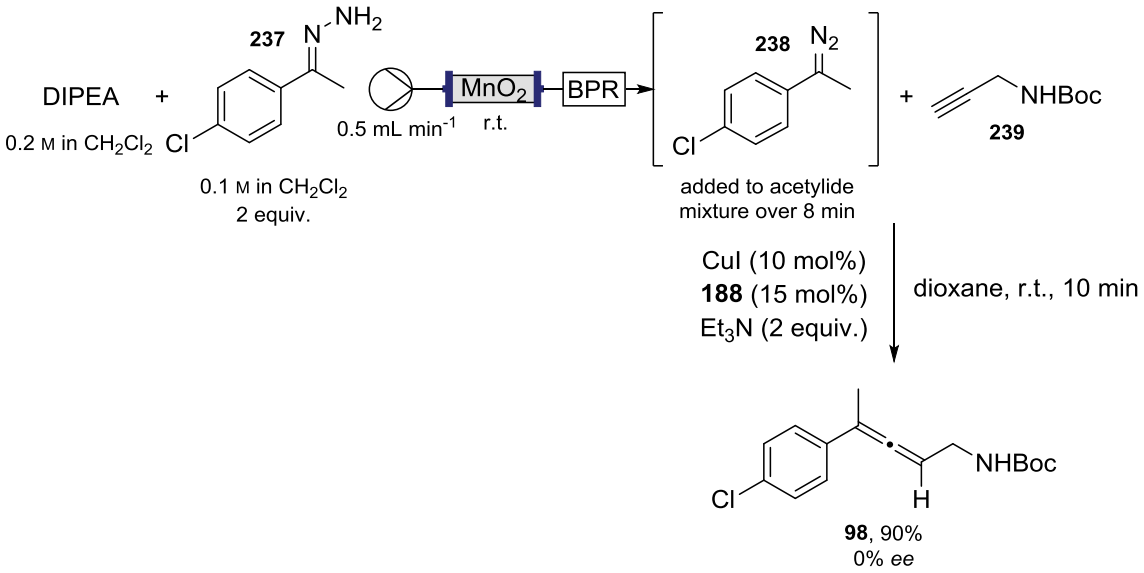
229, 45% (+37%)
95% *ee*



Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product, yields in parentheses are of the alkyne cross-product; *ee* determined by HPLC. * Reaction stirred for 20 min after addition of diazo compound. † Reaction conducted on 5 mmol scale with respect to alkyne.

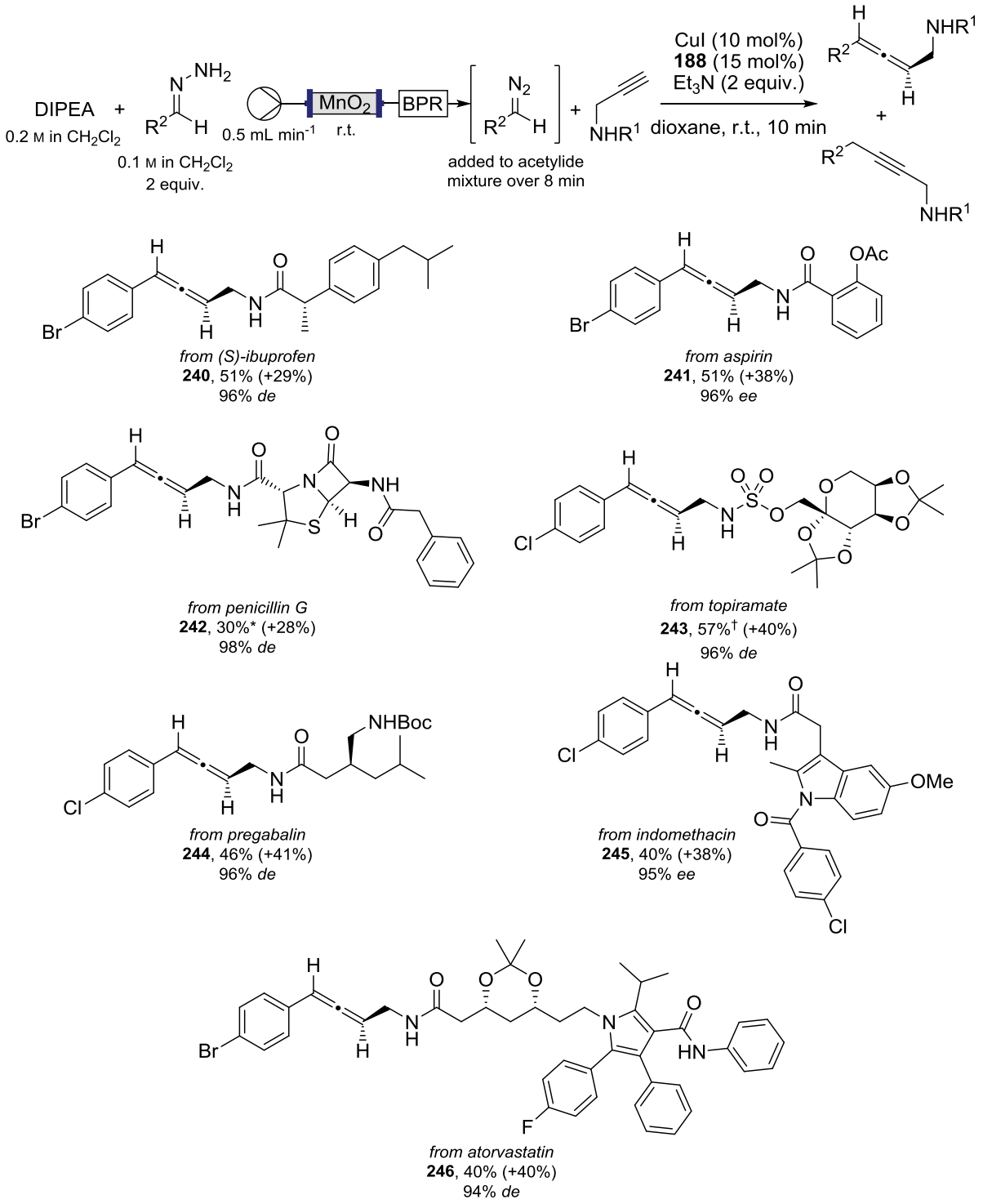
Scheme 94: Disubstituted allene synthesis *via* coupling of aldehyde-derived semi-stabilised diazo compounds and terminal alkynes using CuI catalysis.

When ketone-derived aryl diazo compound **238** was utilised, generated from hydrazone **237** (Scheme 95), no enantioselectivity was observed in the allene cross-product **98** when reacting with *N*-Boc propargylamine (**239**). No alkyne cross-product also was observed in this case, suggesting that tridentate ligand **188** exclusively allows asymmetric allene coupling of aldehyde-derived aryl diazo compounds, contrasting with the bidentate BOX ligand-mediated process described by Wang *et al.*[126] for the asymmetric coupling of ketone-derived aryl diazo compounds.



Scheme 95: Attempted asymmetric coupling of ketone-derived diazo compound **238** with *N*-Boc propargylamine (**239**).

To further probe the effectiveness of the procedure for late-stage functionalisation, a selection of natural products and drug molecules were derivatised to their corresponding propargylamines, then subjected to asymmetric allene coupling (Scheme 96). In most cases, such as in the case with (*S*)-ibuprofen (**240**), aspirin (**241**), topiramate (**243**), pregabalin (**244**), indomethacin (**245**) and atorvastatin (**246**), yields and diastereoselectivities/ enantioselectivities were similar to the previous substrates. For penicillin G, yield of allene **242** was slightly poorer at 30% but diastereoselectivity remained excellent at 98% *de*. Similar to the synthesis of **221** bearing a thiophene moiety (Scheme 94), the thioether functionality may have impeded binding of the alkyne to the catalyst, affecting yield and lengthening reaction time.



Reactions performed on 0.2 mmol scale with respect to terminal alkyne; yields stated are of isolated product, yields in parentheses are of the alkyne cross-product; *de*/*ee* determined by HPLC. * Reaction stirred for 20 min after addition of diazo compound. † Yield by ^{1}H NMR using 1,4-dinitrobenzene as internal standard.

Scheme 96: Late-stage modification of natural products/drug molecules *via* asymmetric allene coupling.

Scale-up to 5 mmol of propargylamide for allene **236** provided 0.89 g of material in 47% yield and 95% *ee*, essentially identical to the smaller scale run. Recrystallisation of this

compound provided crystals that were suitable for analysis by X-ray diffraction (Figure 16), which revealed that the stereochemistry of the new axially chiral centre was (*R*).

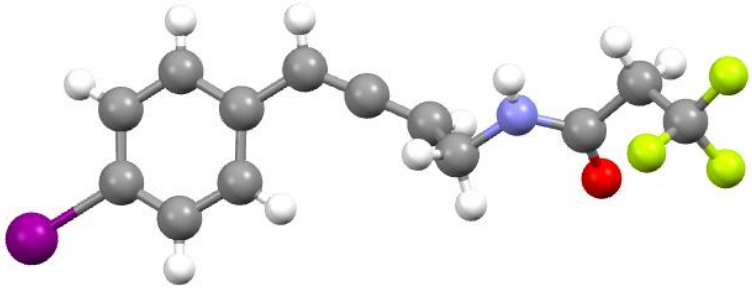


Figure 16: X-ray crystal structure of allene **236**.

Stereochemical assignment of the other allenes synthesised was initially assigned by analogy, but confirmed by the laevorotatory nature of the optical rotations. By use of the Lowe-Brewster rule,[136,137] the aromatic ring attached to the allene is the most polarisable group, leading to an anticlockwise sense (Figure 17). Allene **242** derived from penicillin G was one exception to the laevorotatory optical rotations, with an optical rotation of +2.2. Since the starting material alkyne has a highly dextrorotatory optical rotation of +228.6, it appears that the allene functionality contributes a strongly laevorotatory component (thus consistent with (*R*)-stereochemistry) whilst the remainder of the molecule provides a similar strongly dextrorotatory component.

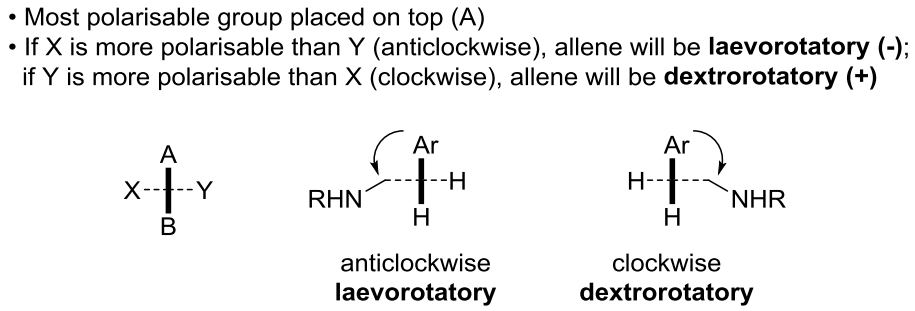


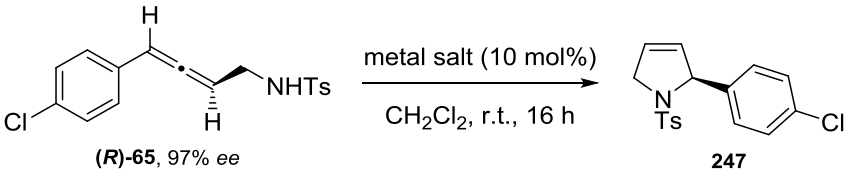
Figure 17: Lowe-Brewster rule as applied to disubstituted allenes.

3.3.5. Pyrroline synthesis using allene **(*R*)-65**

As a demonstration of the use of allenes for cyclisation reactions, various metal catalysts were screened for reaction of allene **(*R*)-65** to form the corresponding 3-pyrroline **247**. Gold catalysts such as AuCl and $AuCl_3$ caused decomposition of the allene (Table 5, entries 1 and

2), whereas the majority of silver catalysts were ineffective in converting starting material (Table 5, entries 3-9). Fortunately, $AgPF_6$ (Table 5, entry 10) was found to be a suitable soluble source of Ag^+ ions, providing the desired pyrroline **247** in quantitative yield and good axial to point chirality transfer (97% to 95% *ee*).

Table 5: Metal catalyst testing for cyclisation of allene **(*R*)-65** to pyrroline **247**.

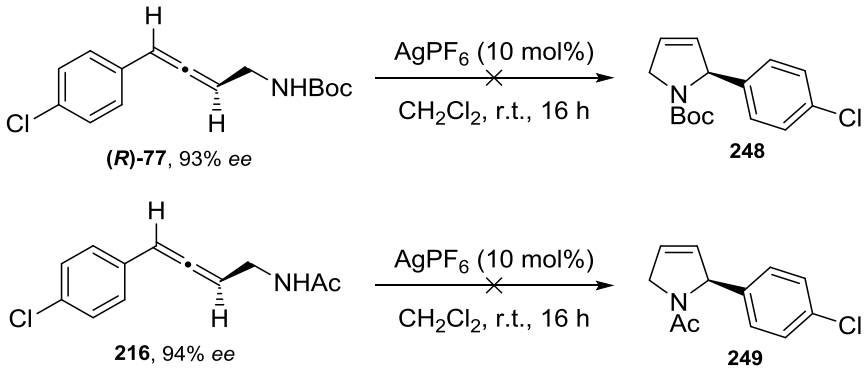


(*R*)-65, 97% *ee* **247**

Entry	Metal salt	Yield* / %	*ee* / %
1	AuCl	(dec.)	
2	$AuCl_3$	(dec.)	
3	Ag_2CO_3	(no reaction)	
4	Ag_2SO_4	(no reaction)	
5	AgOTf	(no reaction)	
6	AgOAc	(no reaction)	
7	$AgNO_3$	(no reaction)	
8	AgOCN	(no reaction)	
9	AgI	(no reaction)	
10	**$AgPF_6$**	**99**	**95**

* Reactions performed on *ca*. 0.05 mmol scale with respect to allene **(*R*)-65**; yields stated are of isolated product; *ee* determined by HPLC.

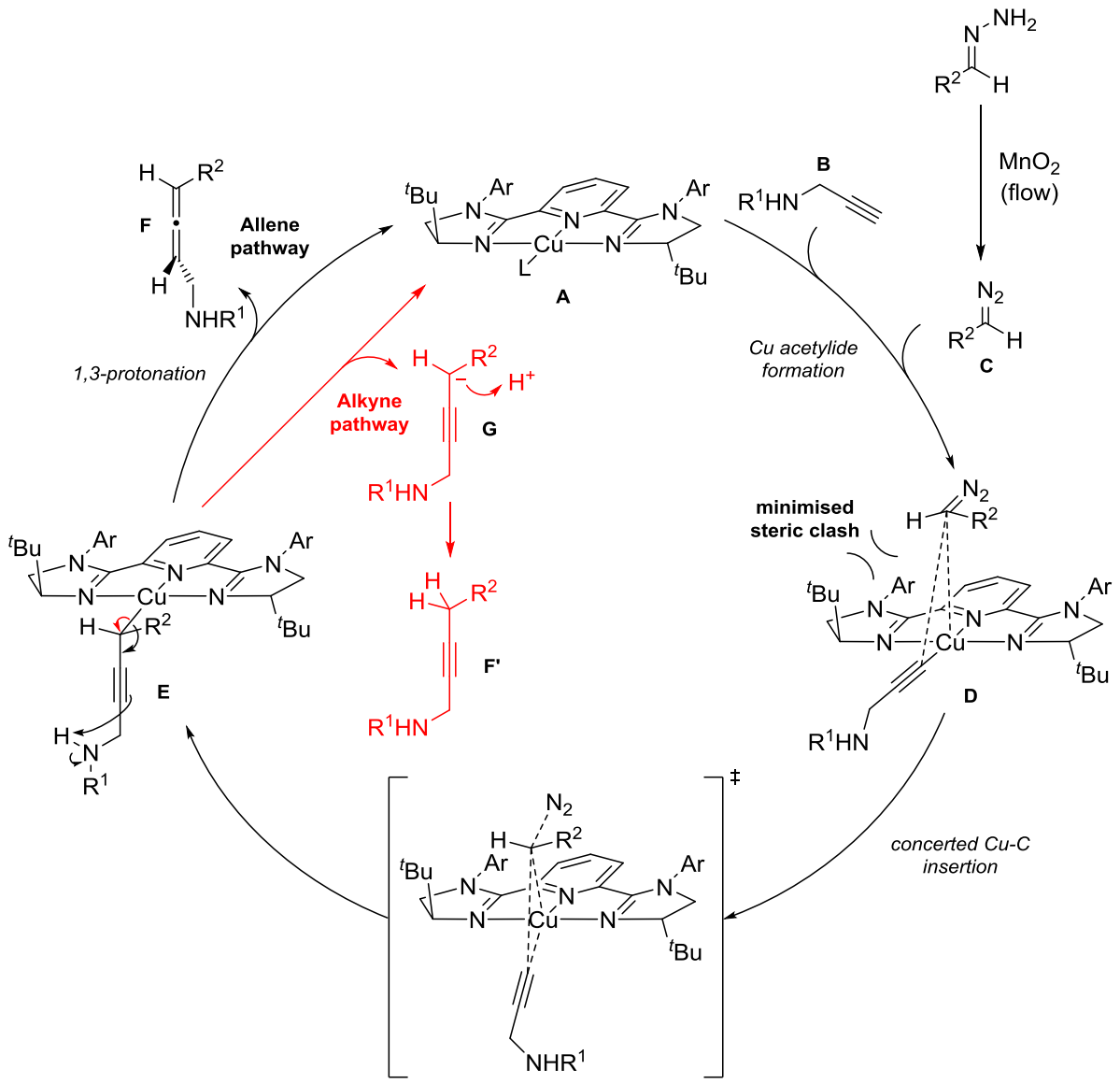
However, the reaction was not found to be general when cyclisation was attempted for the synthesis of pyrrolines **248** and **249**, using the carbamate and amide-based allenes **(*R*)-77** and **216** respectively, with no conversion of the starting material observed (Scheme 97). For these substrates, it is likely that ability of the nitrogen atom to act as a nucleophile is severely curtailed by conjugation into the amide π-system, thus unable to participate in cyclisation as observed with sulfonamide-based allene **(*R*)-65**.



Scheme 97: Attempted cyclisation of allenes **(*R*)-77** and **216** under silver-catalysed conditions.

3.3.6. Mechanistic discussion

The mechanism of the enantioselective asymmetric allene coupling of aldehyde-derived aryl diazo compounds and terminal alkynes is likely to proceed as described below (Scheme 98).



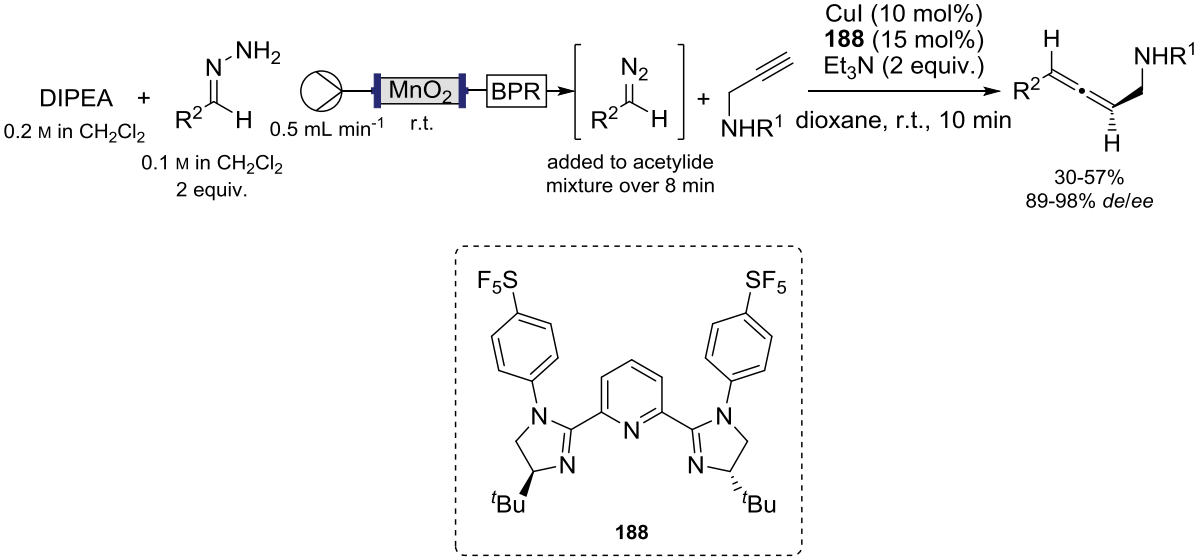
Scheme 98: Proposed mechanism for chiral disubstituted allene formation *via* asymmetric copper-catalysed coupling of aldehyde-derived aryl diazo compounds and terminal alkynes.

In the presence of the ligand-copper(I) complex **A** and base, the terminal alkyne (**B**) forms the copper(I) acetylide complex **D**. Since complex **D** already has 18-electrons in its valence orbitals, attack of diazo compound **C** onto the copper centre is precluded. A possible reaction pathway involves the concerted insertion of the diazo compound into the Cu-C bond of complex **D**, arranged such that the smaller H atom of the diazo compound approaches next to the bulky ^{t}Bu group of the ligand, hence minimising steric clash. This process provides **E**, which can be protonated from the front face of the catalyst to form the desired allene cross-coupled product **F**, with the acidic N-H bond acting as the internal proton source. Migration of copper to an allenylcopper species (Scheme 53) appears unlikely, since protonation of this species would lead to the opposite enantiomer of allene **F**.

For the alkyne cross-coupled product, this could be produced from **E** if dissociation from the ligand-copper(I) complex occurred, resulting in an anion **G** that would then undergo protonation to form **F′**. This appears to be supported by the poorer allene:alkyne ratios observed for electron-withdrawing substituents on the aryl diazo compound, as these anions would be more stabilised and thus lead to more formation of the alkyne cross-coupled product.

3.4. Conclusions and outlook

To summarise, a new PyBIM ligand (**188**) was designed that allowed the copper-catalysed coupling of aldehyde-derived semi-stabilised aryl diazo compounds and propargylated amines, providing disubstituted allenes in moderate yields and high enantioselectivities rapidly and with a wide functional group tolerance (Scheme 99). The versatility of the process was illustrated by the asymmetric allenylation of seven natural products and drug molecules and the utility of these molecules emphasised by converting allene **(*R*)-65** to pyrroline **247** using silver(I) catalysis.



Scheme 99: Summary of chiral disubstituted allene synthesis by asymmetric coupling of flow-generated semi-stabilised diazo compounds and terminal alkynes.

Although there are many advantages to this methodology, a major drawback lies in the formation of significant quantities of the alkyne cross-coupled side product, limiting the scope of the terminal alkyne to appropriately functionalised propargylamine derivatives, as well as leading to generally moderate yields. A potential future line of research could involve

installation of suitably acidic groups on the ligand skeleton on a variable tether length, acting therefore as a bifunctional catalyst that could lead to improved allene:alkyne selectivities and broader substrate scope (Figure 18).

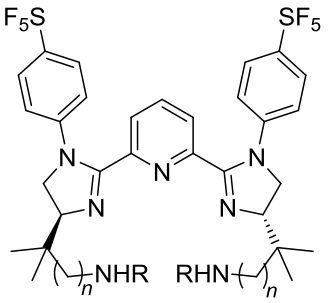


Figure 18: Potential further investigations by installation of acidic N-H moieties.

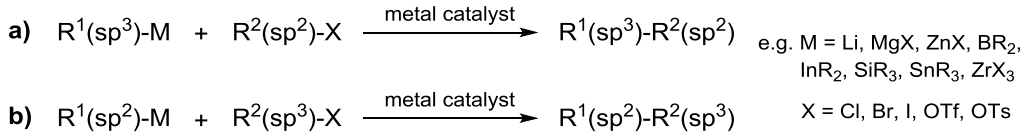
Overall, the advances described in this chapter should enable chemists to easily access chiral disubstituted allenes using a catalytic asymmetric coupling method. Taken together with the complementary asymmetric route to trisubstituted allenes described by Wang *et al.*,[126] it is envisaged that further applications of chiral allenes in organic synthesis can now be readily developed. Furthermore, the advantage of using PyBIM ligands over PyBOX ligands as observed for this methodology could be important for the development of new catalytic asymmetric reactions in organic synthesis.

4. C(sp^2)-C(sp^3) cross-couplings using flow-generated diazo compounds

4.1. C(sp^2)-C(sp^3) cross-couplings

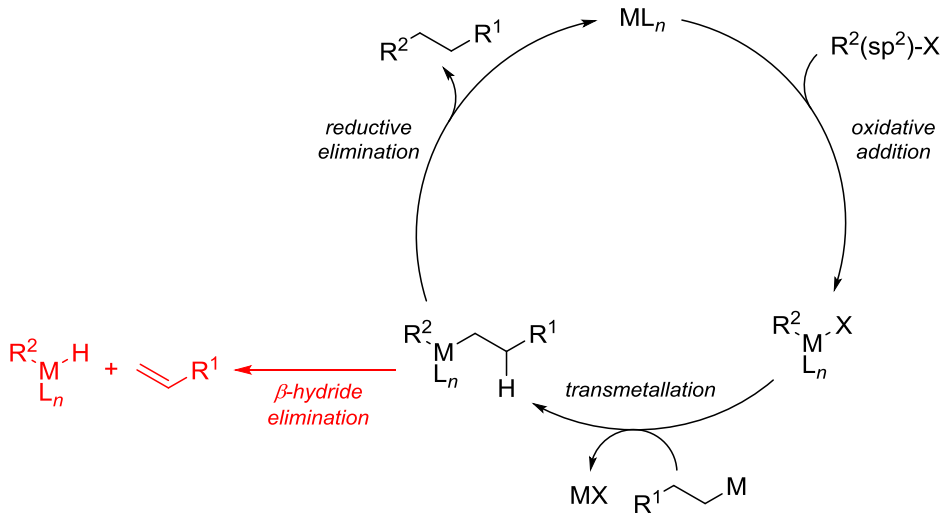
4.1.1. Metal-catalysed C(sp^2)-C(sp^3) cross-couplings

Unlike the well-established metal-catalysed C(sp^2)-C(sp^2) cross-couplings, analogous C(sp^2)-C(sp^3) cross-couplings have proven challenging to develop. These types of metal-catalysed couplings can be separated into two categories (Scheme 100): (a) coupling of a C(sp^3)-based organometallic reagent with a C(sp^2)-based electrophile; and (b) coupling of a C(sp^2)-based organometallic reagent with a C(sp^3)-based electrophile. By far the most common metals utilised for these couplings are palladium or nickel, though copper, iron and cobalt-catalysed couplings are also relatively prevalent.[138]



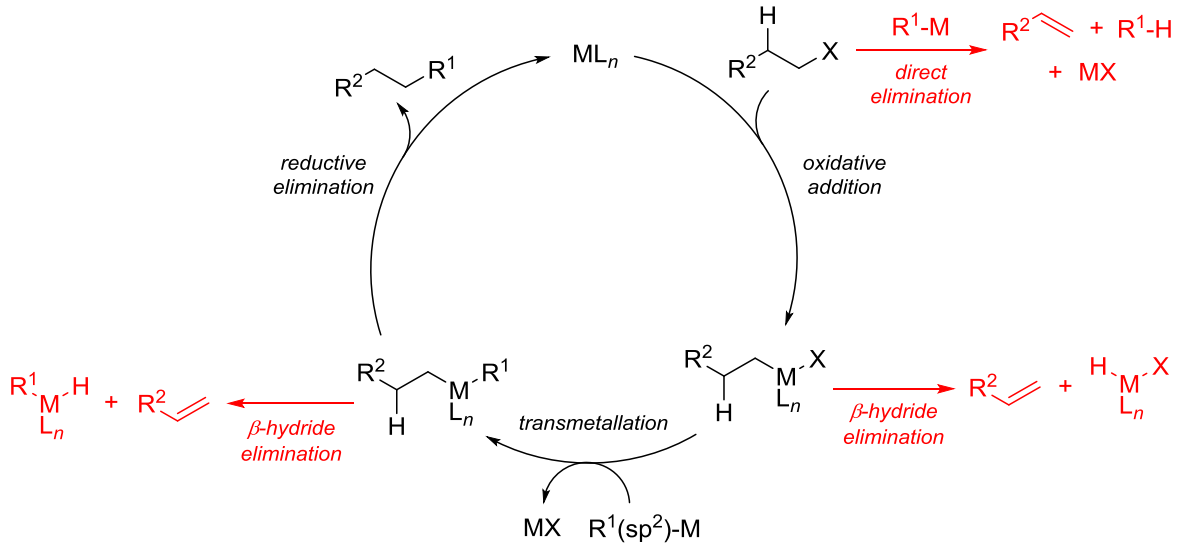
Scheme 100: Approaches to metal-catalysed C(sp^2)-C(sp^3) cross-couplings.

In general, metal-catalysed coupling reactions usually proceed through a three-step cycle, involving an oxidative addition, transmetallation, then reductive elimination. For the first type of C(sp^2)-C(sp^3) cross-couplings involving alkyl-based organometallics, oxidative addition and transmetallation occur smoothly with the aryl/alkenyl-based electrophile. Slow reductive elimination to form the new C-C bond is however a particular problem, since the metal complex is liable to undergo β-hydride elimination and lead to the formation of alkene byproducts, unlike C(sp^2)-C(sp^2) cross-couplings (Scheme 101).[138]



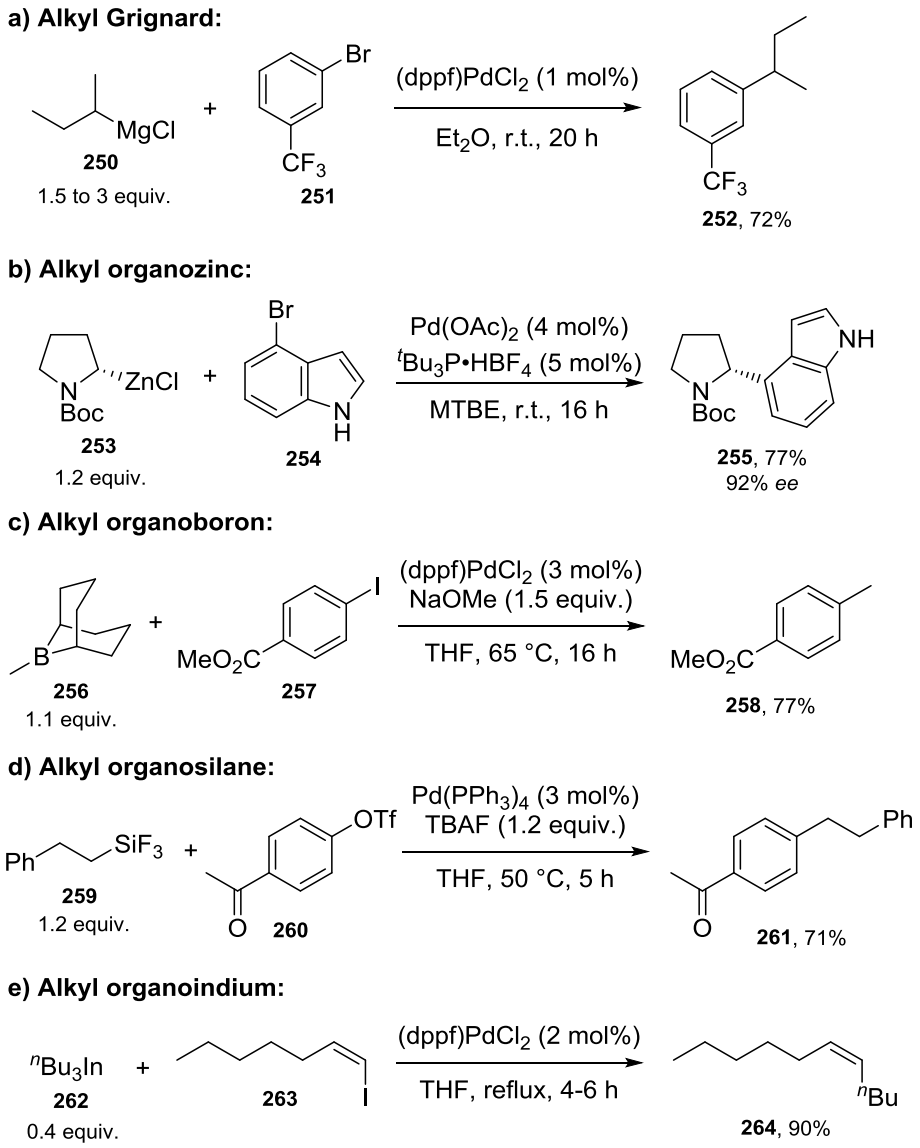
Scheme 101: Catalytic cycle and side-reactions for metal-catalysed coupling of C(sp^3) organometallics with C(sp^2) electrophiles.

For the second, more challenging type of C(sp^2)-C(sp^3) cross-couplings involving alkyl-based electrophiles, the process is further exacerbated by numerous factors. Firstly, oxidative addition of the metal catalyst is slower on unreactive alkyl electrophiles, proceeding usually *via* S_N2 or radical mechanisms rather than the concerted process observed with C(sp^2)-based electrophiles. With strongly basic organometallic reagents (e.g. organolithiums, Grignards), direct elimination of the alkyl electrophile may become a significant side reaction. Secondly, with the use of an alkyl-based electrophile, β-hydride elimination is now a possible side reaction immediately after oxidative addition, and slow transmetallation would lead to significant levels of this process. Finally, as previously mentioned with alkyl-based organometallics, slow reductive elimination also leads to significant β-hydride elimination (Scheme 102).[138]



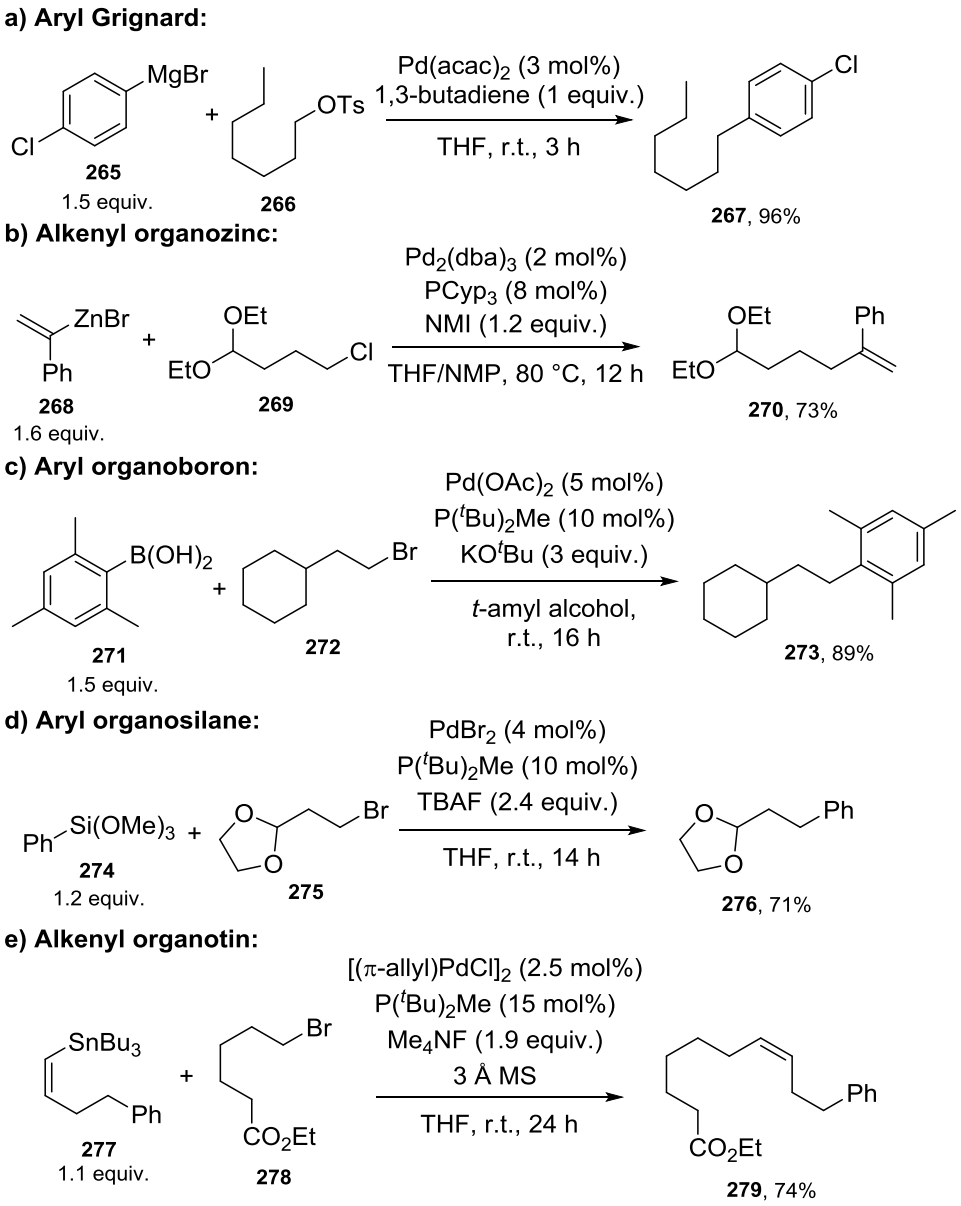
Scheme 102: Catalytic cycle and side-reactions for metal-catalysed coupling of C(sp^2) organometallics with C(sp^3) electrophiles.

For palladium-based catalytic procedures, efforts have primarily focused on coupling alkyl organometallics with aryl/alkenyl electrophiles.[138] A variety of procedures have been described for the coupling of various electrophiles (e.g. **251**, **254**, **257**, **260**, **263**) with alkyl Grignard (e.g. **250**), organozinc (e.g. **253**), organoboron (e.g. **256**), organosilicon (e.g. **259**) and organoindium reagents (e.g. **262**) to access C(sp^2)-C(sp^3) cross-coupled products (e.g. **252**, **255**, **258**, **261**, **264**) (Scheme 103).[139-143] The level of success is primarily dependent on the steric nature of the alkyl organometallic reagent: coupling of primary alkyl organometallics is usually facile and high-yielding, whereas secondary alkyl reagents are more challenging to utilise. In contrast, tertiary alkyl organometallic reagents represent a significant unsolved problem for palladium-based catalysis as a general useful method for coupling these reagents is unknown. These processes require substrate-specific combinations of ligand, base and solvent to effect desired reactivity; in many cases, the use of electron-rich, bulky phosphine ligands are crucial to achieving high rates of reductive elimination, thus suppressing β-hydride elimination.



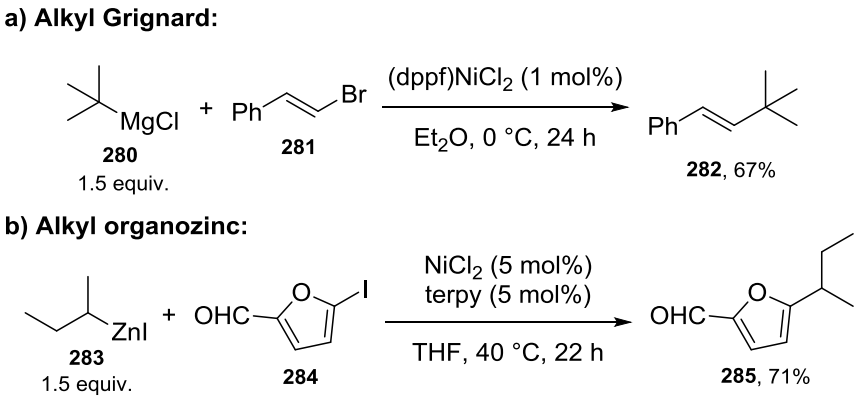
Scheme 103: Selected examples of palladium-catalysed C(sp^2)-C(sp^3) cross-couplings using aryl/alkenyl electrophiles and various alkyl organometallic reagents.[139-143]

The use of unactivated alkyl electrophiles for palladium-mediated analogous C(sp^2)-C(sp^3) cross-coupling remains highly underdeveloped, since only primary alkyl electrophiles (e.g. **266**, **269**, **272**, **275**, **278**) have been coupled with aryl/alkenyl Grignards (e.g. **265**), organozincs (e.g. **268**), organoborons (e.g. **271**), organosilanes (e.g. **274**) and organostannanes (e.g. **277**) successfully thus far for C(sp^2)-C(sp^3) cross-coupled products (e.g. **267**, **270**, **273**, **276**, **279**) (Scheme 104).[144-148] Palladium-catalysed routes are generally limited to the S_N2 mechanism of oxidative addition, hence oxidative addition to unactivated secondary and tertiary alkyl electrophiles becomes too slow to allow productive coupling processes.



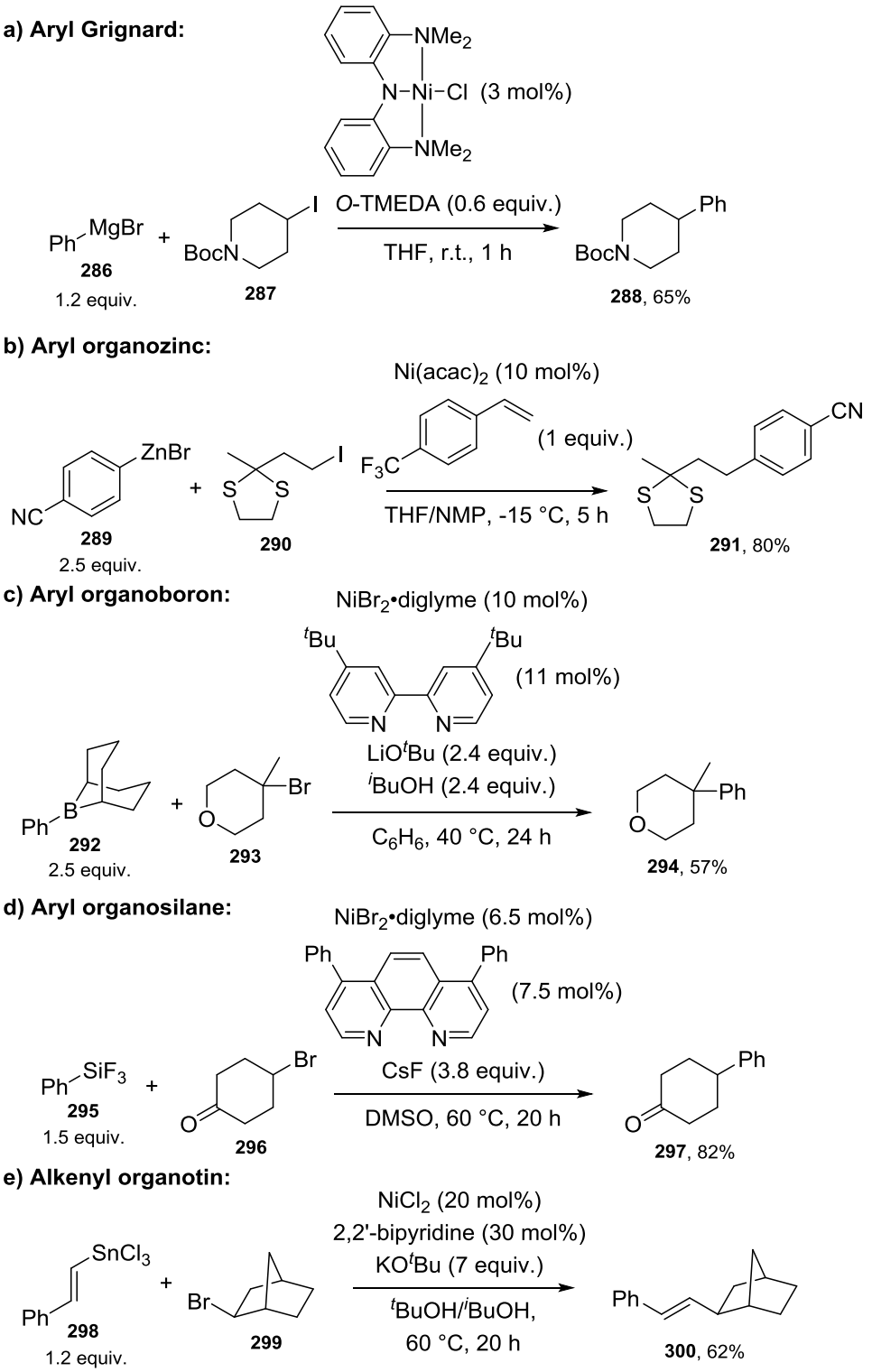
Scheme 104: Selected examples of palladium-catalysed C(sp^2)-C(sp^3) cross-couplings using unactivated alkyl electrophiles and various aryl/alkenyl organometallic reagents.[144-148]

In contrast to palladium-catalysed methods, processes using nickel catalysis for coupling C(sp^3) organometallics (e.g. **280**, **283**) with C(sp^2) electrophiles (e.g. **281**, **284**) are able to tolerate primary, secondary and even tertiary alkyl nucleophiles to generate cross-coupled products (e.g. **282**, **285**), although these methods are generally limited to the use of alkyl Grignard and organozinc reagents (Scheme 105).[149,150]



Scheme 105: Selected examples of nickel-catalysed C(sp^2)-C(sp^3) cross-couplings using aryl/alkenyl electrophiles and various alkyl organometallic reagents.[149,150]

Nickel-based catalytic cycles, unlike palladium-mediated processes, can proceed *via* radical mechanisms due to the ability of nickel to gain or lose single electrons, interchanging usually between four different oxidation states, i.e. Ni^0, Ni^I, Ni^{II} and Ni^{III}, unlike the Pd^0/Pd^{II} and Pd^{II}/Pd^{IV} cycles observed for palladium catalysis. With this different mode of reactivity, oxidative addition is no longer limited to S_N2 processes and thus unactivated alkyl halides spanning primary (e.g. **290**), secondary (e.g. **287**, **296**, **299**) and tertiary halides (e.g. **293**) become permissible reagents for C(sp^2)-C(sp^3) cross-coupling with aryl/alkenyl organometallic reagents (e.g. **286**, **289**, **292**, **295**, **298**) to access the corresponding cross-coupled products (e.g. **288**, **291**, **294**, **297**, **300**) (Scheme 106).[151-155]



Scheme 106: Selected examples of nickel-catalysed C(sp^2)-C(sp^3) cross-couplings using unactivated alkyl electrophiles and various aryl/alkenyl organometallic reagents.[151-155]

In addition, nickel catalysis has been shown to be highly useful for C(sp^2)-C(sp^3) cross-coupling when utilised in tandem with methods generating carbon-centred radicals, for example photoredox catalysis (enabling the coupling of reagents such as oxalates, carboxylic

acids and organoboronates),[156-162] redox-active esters[163-165] and Katritzky pyridinium salts[166] (Figure 19).

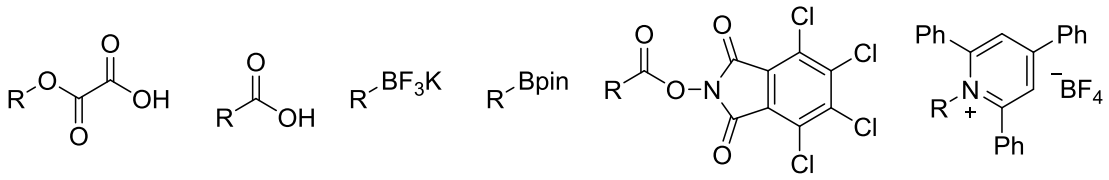
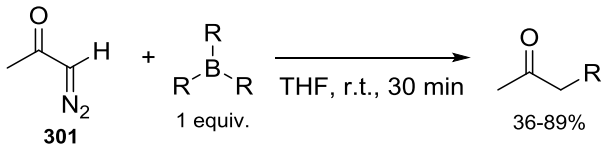


Figure 19: Examples of precursors to carbon-centred radicals for application in nickel-catalysed cross-coupling reactions.

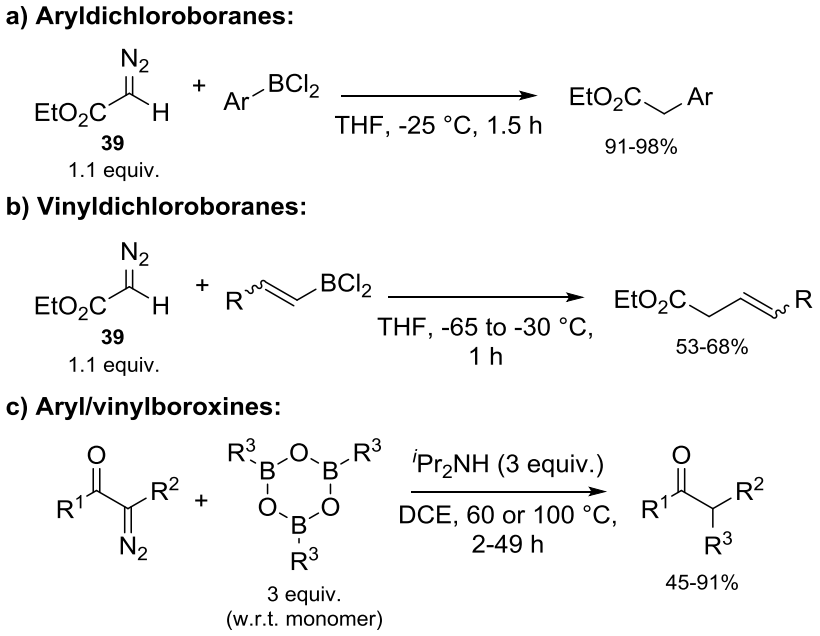
4.1.2. Metal-free C(sp^2)-C(sp^3) cross-couplings using diazo compounds

Although developments in C-C bond-forming cross-couplings have predominantly involved metal catalysis, a valuable alternative approach involves the use of diazo compounds and their reactions with organoboron derivatives for metal-free coupling processes. In 1968, Hooz and Linke described the reaction of the stabilised diazo compound, diazoacetone (**301**), with trialkylboranes, thus providing a route to C(sp^3)-C(sp^3) coupled products in a metal-free fashion (Scheme 107).[167]



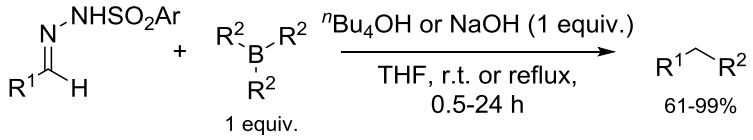
Scheme 107: Coupling of diazoacetone (**301**) with trialkylboranes as reported by Hooz and Linke.[167]

Analogous processes using aryl/vinyl-based organoboronic reagents,[168] such as utilising aryl- and vinyldichloroboranes and aryl/vinylboroxines were subsequently developed, coupling stabilised α-diazocarbonyl compounds (Scheme 108).[169-171] Whilst these reports represented a significant development in methods for metal-free C(sp^2)-C(sp^3) coupling, they were limited to stabilised α-diazocarbonyl compounds.



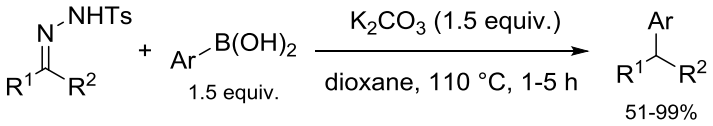
Scheme 108: Coupling of stabilised α-diazocarbonyl compounds with aryldichloroboranes, vinyldichloroboranes and aryl/vinylboroxines as reported by Hooz *et al*.,[169] Brown and Salunkhe,[170] and Wang *et al*.[171] respectively.

A major first step in generalising the scope to less stabilised diazo compound partners was made by Kabalka *et al*. in 1994, when the coupling of trialkylboranes and aryl aldehyde-derived sulfonylhydrazones was described (Scheme 109).[172] A significant limitation of this process involves the use of oxygen-sensitive trialkylboranes, as well as poor atom efficiency arising from only one of the three alkyl groups being transferred in this process.



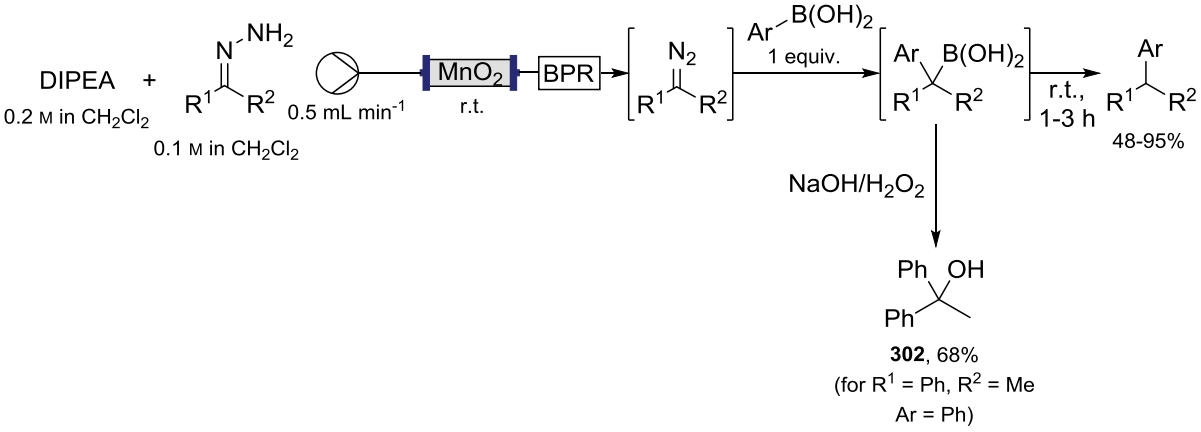
Scheme 109: Coupling of aryl aldehyde-derived sulfonylhydrazones with trialkylboranes as reported by Kabalka *et al*.[172]

A further report by Barluenga *et al*. in 2009 involved the use of readily available arylboronic acids coupling with tosylhydrazones (Scheme 110).[173] After this seminal publication, subsequent reports based on generalising this process for utilising vinylboronic acids[174] and saturated heterocyclic sulfonylhydrazones,[24] as well as application to medicinal chemistry programmes[175] and flow processes,[176] have highlighted its utility. However, major drawbacks of the procedure have also been identified, including protodeboronation of starting boronic acid material and elimination, due to the high temperature and basic conditions required for diazo generation from sulfonylhydrazones.



Scheme 110: Coupling of tosylhydrazones with arylboronic acids as reported by Barluenga *et al.*[173]

These problems were addressed to some extent by Ley *et al.*, where a flow process for the mild generation of semi-stabilised aryl- and vinyl diazo compounds from their corresponding aryl/vinyl hydrazones was reported *via* activated MnO_2 oxidation, thus allowing these C(sp^2)-C(sp^3) cross-couplings to occur at ambient conditions (Scheme 111).[65] Interception of the putative, unstable boronic acid intermediate has also been demonstrated, a key advantage that is not possible using the original conditions reported by Barluenga *et al.*; thus, treatment of transient intermediate with H_2O_2/NaOH leads to the corresponding alcohol (e.g. **302**), whereas addition of further diazo compounds allows multiple C-C bond formation in an iterative fashion.[66]



Scheme 111: Coupling of semi-stabilised aryl- and vinyl diazo compounds with arylboronic acids as reported by Ley *et al.*[65]

These findings represent a noteworthy milestone in the development of metal-free cross-coupling methods. However, a major drawback still exists for this process: the generation of diazo compounds *via* this route is strictly limited to semi-stabilised diazo compounds, i.e. 'activated' aryl- and vinylhydrazones that are amenable to oxidation by MnO_2. The mild generation of non-stabilised diazo compounds is impossible using this route. Hence, a mild route towards these highly sought compounds would be extremely valuable, not only for expanding the scope of the metal-free C(sp^2)-C(sp^3) coupling process, but also potentially providing access to new alcohols, boronic acid/ester reagents and iterative coupling products.

4.2. Aims of the project

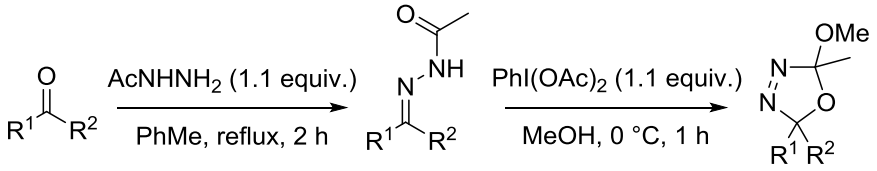
Although methods to generate solutions of semi-stabilised diazo compounds have been established, as well as illustrating their use in metal-free C(sp^2)-C(sp^3) cross-coupling reactions,[65] mild and general procedures for the generation of non-stabilised diazo compounds have been underdeveloped. The aim of this project thus focuses on two goals: (a) to identify a suitable precursor for generation of non-stabilised diazo compounds, using a sufficiently mild, general and simple procedure; and (b) to illustrate the use of these diazo compounds by reaction with arylboronic acids in metal-free C(sp^2)-C(sp^3) cross-coupling reactions (Scheme 112).

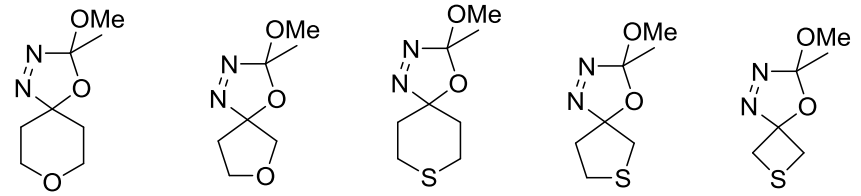
Scheme 112: Investigating the generation of non-stabilised diazo compounds from appropriate precursors and their use in metal-free C(sp^2)-C(sp^3) cross-coupling.

4.3. Results and discussion

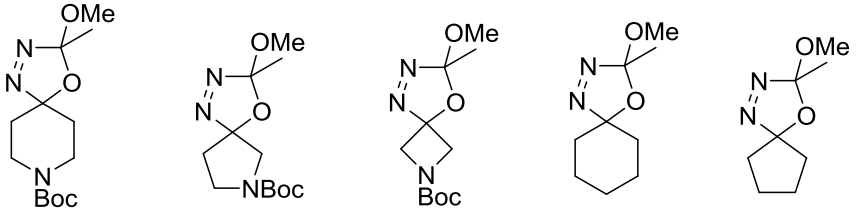
4.3.1. Optimisation results

With the aim of creating a method to allow metal-free C(sp^2)-C(sp^3) coupling using non-stabilised diazo compounds, an appropriate precursor was required, one that would unveil the desired diazo compound under mild conditions. Of the methods surveyed previously (Chapter 1), only three methods appeared appropriate: the base-mediated fragmentation of nitrosoamide derivatives, the oxidation of hydrazones and the photolysis of oxadiazolines. The photolysis method seemed to be the most convenient to test. The starting materials were generally synthesised by a simple two-step, one-pot process from readily available ketones (*via* condensation with acethydrazide then subsequent oxidation using $PhI(OAc)_2$) to provide the desired, bench-stable diazo precursors (**303-324**) (Scheme 113).[42] In addition, utilisation of flow technologies would provide a direct benefit by providing more efficient irradiation, arising from smaller penetration depths compared to a similar scale batch protocol.[177] In contrast, the alternative two approaches for generating diazo compounds require tedious multi-step synthetic routes and lead to relatively unstable diazo precursors.

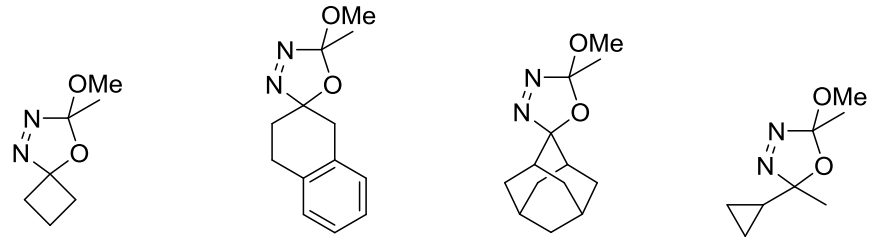




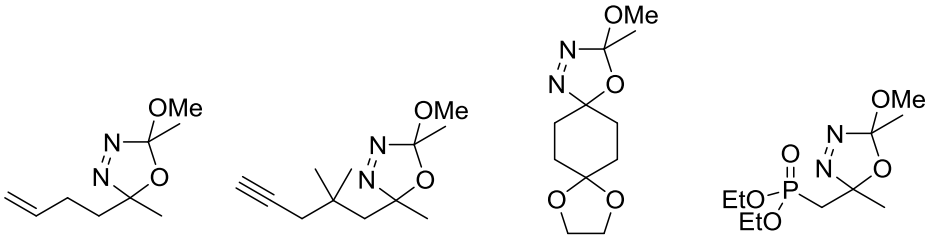
303, 86% **304**, 71%, 1:1 *dr* **305**, 78% **306**, 61%, 1:1 *dr* **307**, 30%



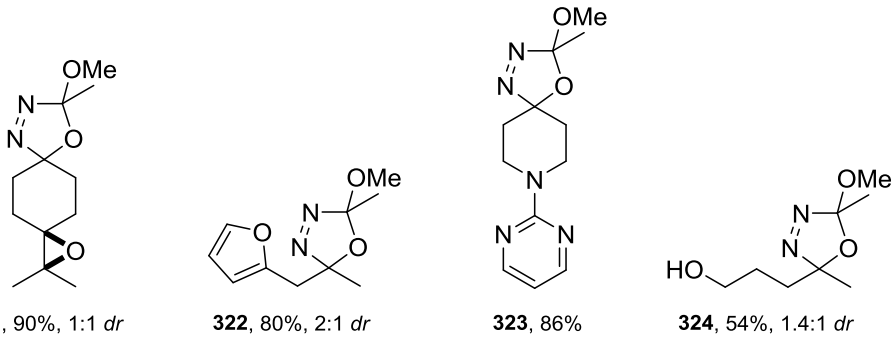
308, 76% **309**, 77%, 1:1 *dr* **310**, 25% **311**, 80% **312**, 94%



313, 48% **314**, 87%, 1:1 *dr* **315**, 80% **316**, 80%, 1:1 *dr*



317, 67%, 1.5:1 *dr* **318**, 81%, 1:1 *dr* **319**, 81% **320**, 59%, 1.5:1 *dr*

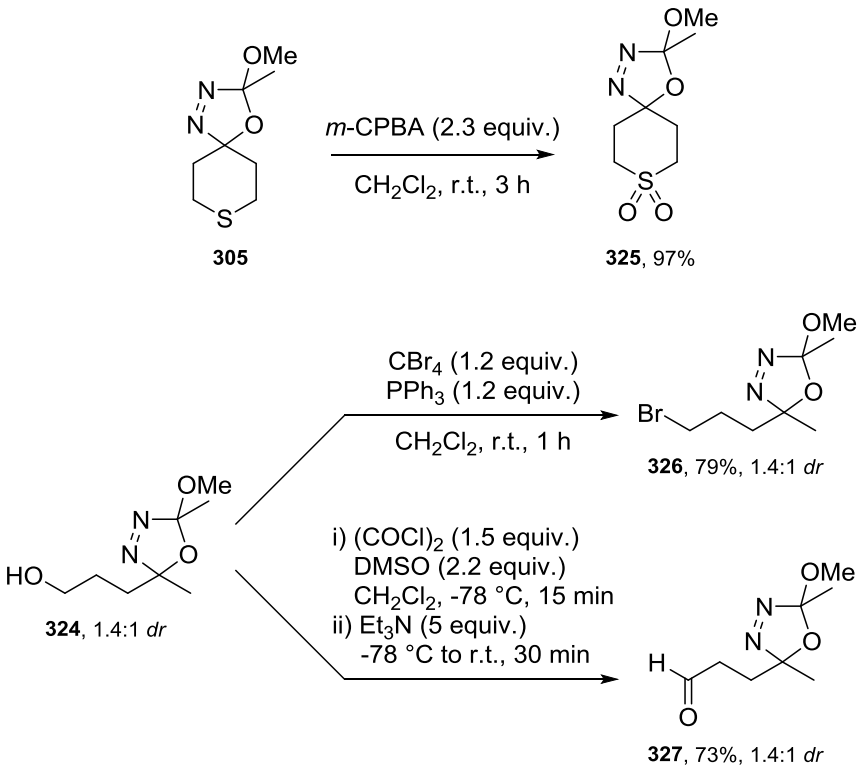


321, 90%, 1:1 *dr* **322**, 80%, 2:1 *dr* **323**, 86% **324**, 54%, 1.4:1 *dr*

Yields stated are of isolated product for the two-step hydrazone formation/oxidation sequence; diastereomeric ratios determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 113: Synthetic route towards 1,3,4-oxadiazolines for use as diazo compound precursors.

In general the two-step yields were moderate to excellent, except for the 4-membered ring precursors **307**, **310** and **313** where significant hydrolysis of the hydrazones by acetic acid was observed in the oxidation step. Oxadiazoline **325** was obtained from the *m*-CPBA mediated oxidation of **305**, whereas oxadiazolines **326** and **327** were obtained by bromination *via* an Appel reaction and Swern oxidation of **324** respectively (Scheme 114).



Scheme 114: Synthesis of oxadiazolines **325**, **326** and **327**.

Using diazo precursor **303**, an initial attempt to produce the corresponding non-stabilised diazo compound **328** involved passing a 0.1 M Et_2O solution of **303** through a 10 mL coil (FEP tubing) at a 0.125 mL min^{-1} flow rate (80 min residence time), irradiated at 310 nm by a 9 W UV lamp on a Vapourtec E-series flow platform. Indeed, in-line IR analysis indicated two identifiable signals, one at 2040 cm^{-1} corresponding to the diazo stretch for compound **328**, along with one at 1746 cm^{-1} corresponding to the C=O stretch of MeOAc (Figure 20). The IR signal for MeOAc was particularly useful for gauging photolytic conversion of any oxadiazoline derived from acetic hydrazide.

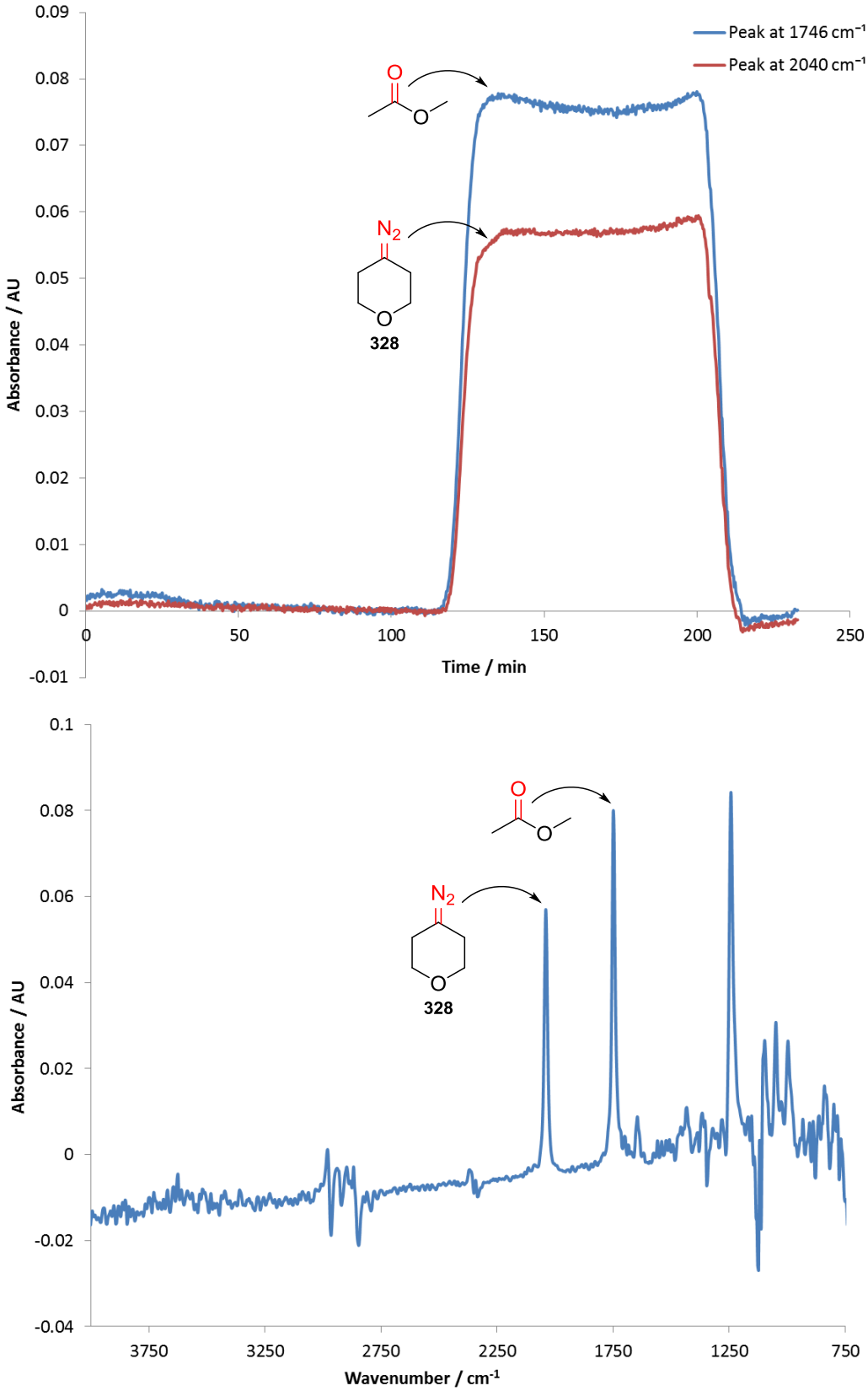
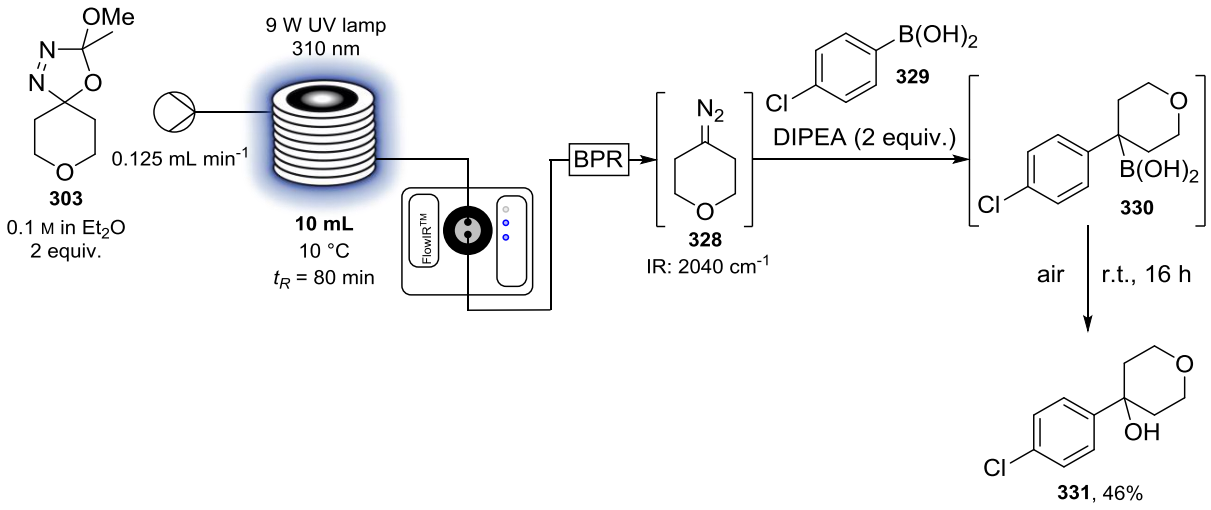


Figure 20: Tracking photolysis of oxadiazoline **303** using in-line IR spectroscopy (top); IR spectrum of reaction mixture at 175 min, showing the presence of diazo compound **328** and MeOAc (bottom).

With the intermediacy of diazo compound **328** confirmed, the reactor output (2 equiv. with respect to oxadiazoline **303**) was directed into a solution of 4-chlorophenylboronic acid (**329**, 1 equiv.) and DIPEA (2 equiv.), then stirred at r.t. under air overnight. Tertiary alcohol **331**, arising from spontaneous atmospheric oxidation of the putative boronic acid intermediate **330**, was thus obtained in 46% yield (Scheme 115).

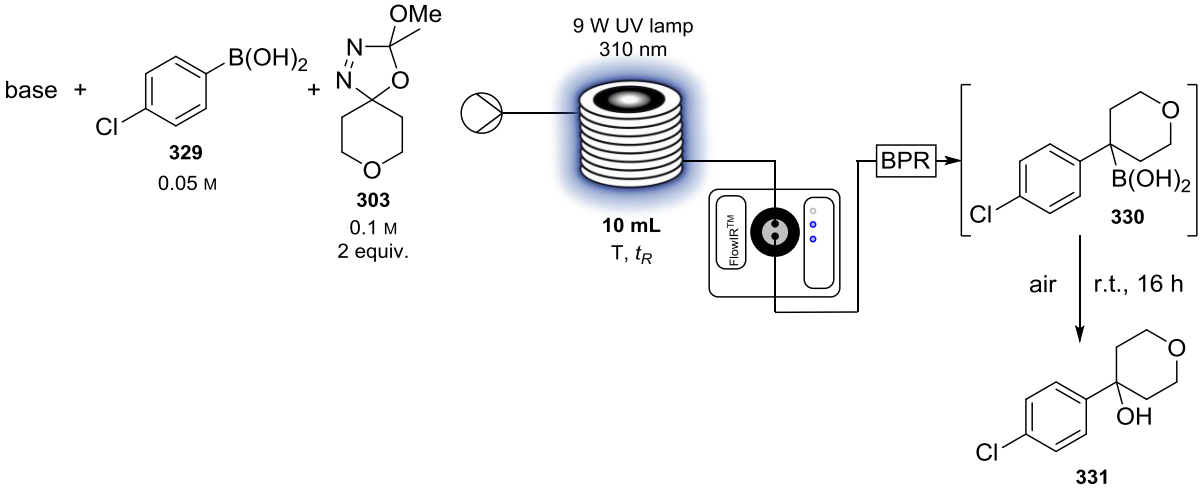


Scheme 115: Initial attempt at *ex situ* generation of diazo compound **328** from photolysis of oxadiazoline **303** and subsequent interception with 4-chlorophenylboronic acid (**329**).

Freshly prepared solutions of diazo compound **328** appeared to lose their distinctive red colouration over a period of 1 to 2 hours, suggesting that conducting an *in situ* photolysis, i.e. passing a combined mixture of boronic acid **329**, oxadiazoline **303** and DIPEA through the photolysis reactor, could be more effective. When this *in situ* protocol was conducted, alcohol **331** was obtained in slightly higher yield, at 55% (Table 6, entry 2). A switch of solvent to CH_2Cl_2 provided 18% when conducted *ex situ* (Table 6, entry 3), but a significantly higher *in situ* yield of 76% (Table 6, entry 4); it is probable that the Et_2O solvent used previously coordinates with the boronic acid or related species (see Section 4.3.3) and leads to poorer interception of highly reactive diazo compound **328**, whereas use of CH_2Cl_2 is advantageous due to the absence of this effect. Variation of other parameters led to decreased yields compared to this entry: a decrease in residence time to 40 min led to slightly lower yield of **331** at 68% (Table 6, entry 5), due to incomplete photolysis of oxadiazoline **303**; utilisation of less DIPEA (1 equiv.) led to a lower 70% yield of **331** (Table 6, entry 6); whereas use of a different base (1,1,3,3-tetramethylguanidine (**15**), Table 6, entry 7) led to complete loss of reactivity, probably due to irreversible coordination of the base to boronic acid **329**.

Changing the photolysis reactor temperature to lower temperatures (0 °C and -10 °C) had no appreciable effect on reaction yield (Table 6, entries 8 and 9), so the original temperature was maintained for reaction scope studies.

Table 6: Optimisation for oxidative C(sp^2)-C(sp^3) cross-coupling of arylboronic acids with non-stabilised diazo compounds generated *via* photolysis of oxadiazolines.

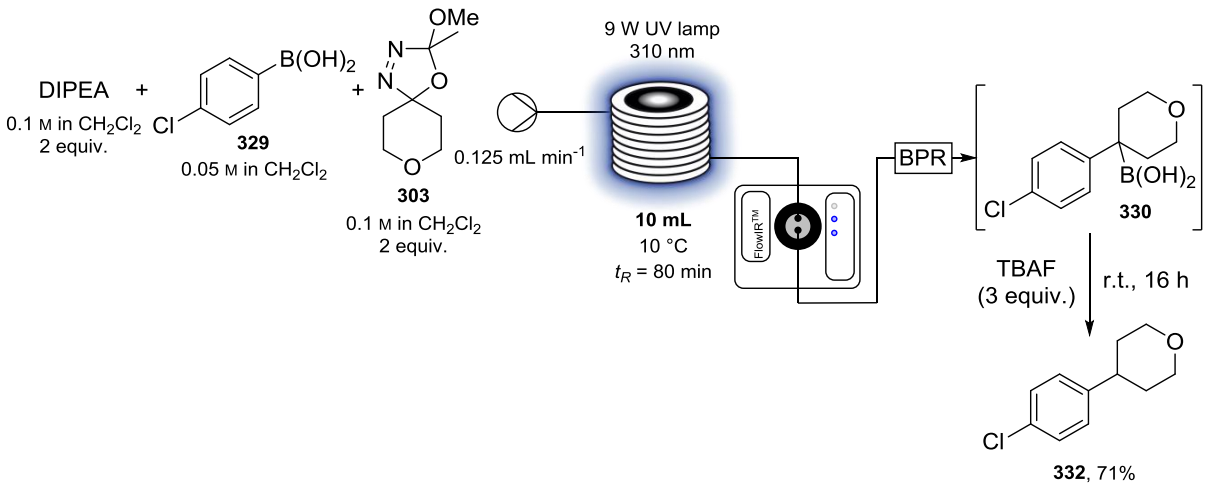


Entry	T / °C	Base	Solvent	t_R / min	Yield* / %	Other comments
1	10	DIPEA (2 equiv.)	Et_2O	80	46	*ex situ*
2	10	DIPEA (2 equiv.)	Et_2O	80	55	-
3	10	DIPEA (2 equiv.)	CH_2Cl_2	80	18	*ex situ*
4	**10**	**DIPEA (2 equiv.)**	**CH_2Cl_2**	**80**	**76**	**-**
5	10	DIPEA (2 equiv.)	CH_2Cl_2	40	68	-
6	10	DIPEA (1 equiv.)	CH_2Cl_2	80	70	-
7	10	TMG (2 equiv.)	Et_2O	80	traces	-
8	0	DIPEA (2 equiv.)	CH_2Cl_2	80	75	-
9	-10	DIPEA (2 equiv.)	CH_2Cl_2	80	76	-

* Reactions performed on 0.5 mmol scale with respect to arylboronic acid; yields stated are of isolated product.

It was notable that during these optimisation studies, the obtained product was oxidised C(sp^2)-C(sp^3) coupling product **331**, with no traces of the protodeboronated product. The sensitivity of tertiary alkyl boronic acids to atmospheric oxidation is known, as well as the difficulty of obtaining deboronated products from these boronic acid substrates.[178] When protodeboronation of boronic acid intermediate **330** was attempted with degassed aqueous HCl or NaOH solutions, no protodeboronated product was observed and only the oxidised product was obtained on re-exposure to air. A report by Aggarwal *et al*. indicated that protodeboronation of tertiary boronic pinacol esters was possible by using TBAF;[179] thus,

when the reaction output was directed into a solution of TBAF and stirred at r.t. overnight, protodeboronated C(sp^2)-C(sp^3) coupling product **332** was finally obtained in 71% yield (Scheme 116).



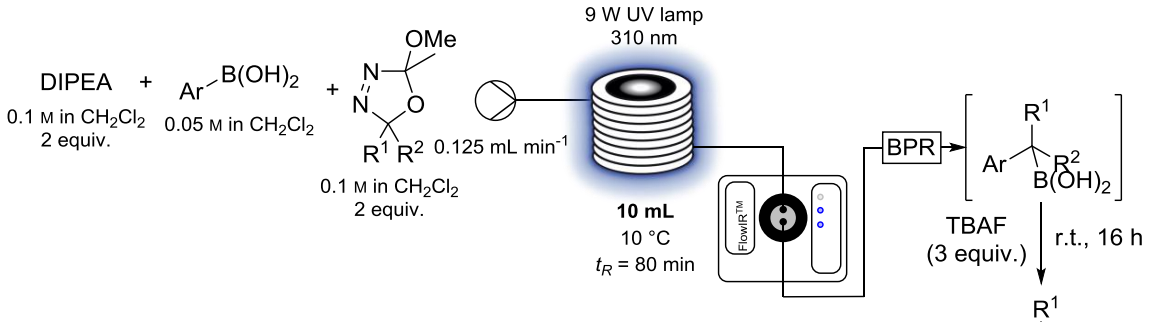
Scheme 116: Switchable 'workup' procedure using TBAF for protodeboronative C(sp^2)-C(sp^3) cross-coupling of arylboronic acids with non-stabilised diazo compounds.

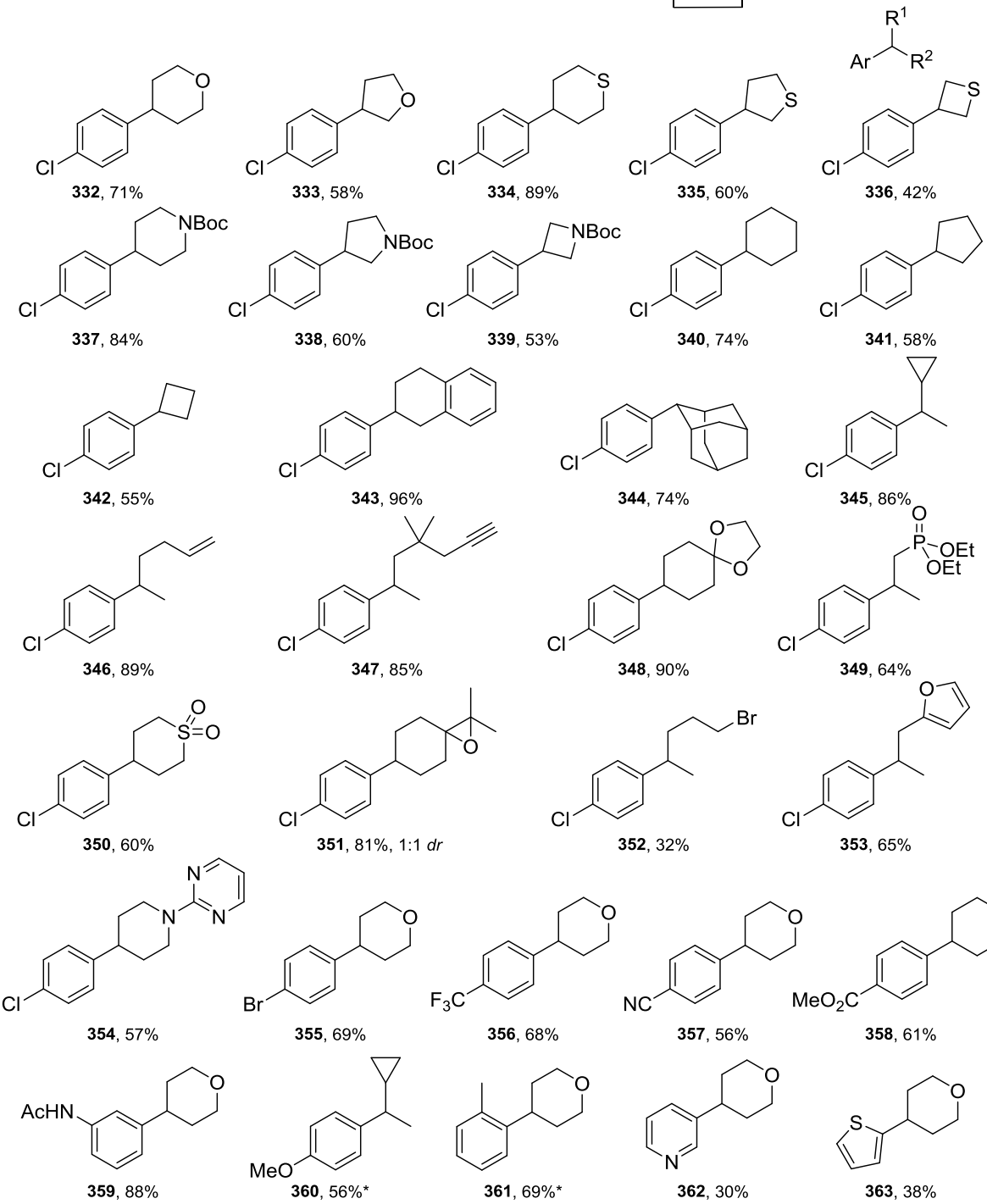
4.3.2. Reaction scope

With methods for both the oxidative and protodeboronative C(sp^2)-C(sp^3) coupling in hand, a full assessment of the reaction scope for arylboronic acids and oxadiazolines was made.[§]

For the protodeboronative C(sp^2)-C(sp^3) coupling with respect to the oxadiazoline component (Scheme 117), a variety of 6-membered, 5-membered and 4-membered, saturated heterocyclic and carbocyclic rings were tolerated, including pyran (**332**), tetrahydrofuran (**333**), tetrahydrothiopyran (**334**), tetrahydrothiophene (**335**), thietane (**336**), *N*-Boc piperidine (**337**), *N*-Boc pyrrolidine (**338**), *N*-Boc azetidine (**339**), cyclohexane (**340**), cyclopentane (**341**) and cyclobutane (**342**) rings. Progressively higher yields were obtained on changing ring size from 4-rings to 5-rings to 6-rings, consistent with progressively more stable diazo compounds with larger ring sizes. The lower stability of the 4-membered diazo compounds can be explained by their strong tendency to react with electrophiles, leading to relief of ring strain by moving from a sp^2-carbon centre to sp^3.

[§] This work was conducted in collaboration with Dr Andreas Greb.

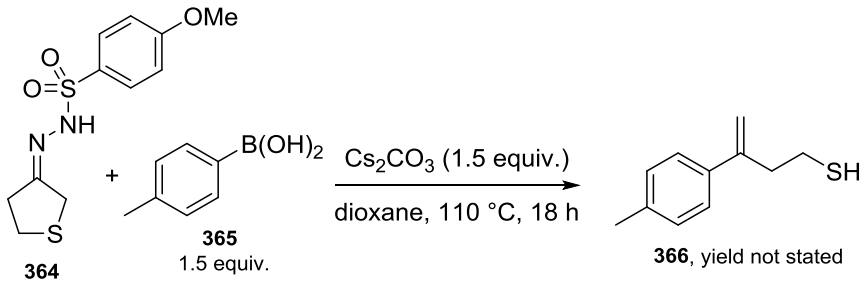




Reactions performed on 0.5 mmol scale with respect to arylboronic acid; yields stated are of isolated product.
* Protodeboronation conducted at 75 °C.

Scheme 117: Protodeboronative C(sp^2)-C(sp^3) coupling using oxadiazolines and arylboronic acids.

Despite this latent instability, it is notable that the 4-membered protodeboronated products (**336**, **339**, **342**) were still obtained in moderate yields, even though the instability of diazocyclobutane (**12**) has been previously reported.[23] In addition, whilst extensive elimination was observed for the tetrahydrothiophene and thietane moieties when sulfonylhydrazones (e.g. **364**) were used for coupling with boronic acids (e.g. **365**), the milder conditions used here for diazo compound generation provided good yields of coupled products **335** and **336** without any of the previously reported olefinic thiol side-products (e.g. **366**) (Scheme 118).[24]



Scheme 118: Unsuccessful C(sp^2)-C(sp^3) cross-coupling of tetrahydrothiophene-derived sulfonylhydrazone **364** with boronic acid **365** due to elimination to **366** as reported by Ley *et al.*[24]

Probing further, oxadiazolines derived from 2-tetralone (**314**) and highly hindered adamantanone (**315**) provided excellent yields of coupling products **343** and **344** respectively. Use of the oxadiazoline derived from cyclopropyl methyl ketone (**316**) allowed the formation of **345** in 86% yield, suggesting that the coupling process (i.e. steps after photolysis of the oxadiazoline has completed) does not occur *via* a radical mechanism due to the absence of cyclopropane ring-opened products, despite the photolytic conditions used.

In terms of functional group compatibility for the oxadiazolines, a myriad of moieties were tolerated, including terminal olefins (**346**), alkynes (**347**), acetals (**348**), phosphonates (**349**) and sulfones (**350**). The use of an epoxide was also possible, providing a 1:1 diastereomeric mixture of product **351** in 81% yield. The use of alkyl bromide **326** was possible, providing 32% yield of **352**, with the lower yield attributed to partial elimination of the product in the presence of TBAF. In contrast, use of alkyl aldehyde **327** led to extensive polymerisation, likely due to TBAF acting as a base and thus enabling aldol reactions. An unprotected primary alcohol substrate **324** was also not viable in this process (Figure 21). Heterocyclic compounds such as furans and pyrimidines were tolerated, providing products **353** and **354** in 65% and 57% yields respectively.

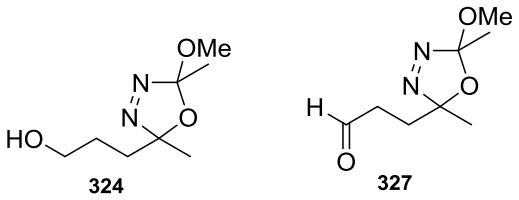


Figure 21: Unsuccessful oxadiazoline examples for protodeboronative C(sp^2)-C(sp^3) cross-coupling.

For scope of the arylboronic acid component, electron-deficient arenes performed well, with 4-bromo (**355**), 4-trifluoromethyl (**356**), 4-cyano (**357**) and 4-methoxycarbonyl (**358**) substituents providing moderate to good yields of coupled products. A relatively more electron-rich arene substrate with 3-NHAc worked well, providing 88% yield of coupling product **359**. In contrast, when 4-methoxybenzeneboronic acid was used, no coupling products were observed using the unmodified general protocol; however, on heating the reaction output with TBAF at 75 °C, coupling product **360** was obtained in 56% yield, suggesting that protodeboronation was more difficult in this particular case. A similar effect was observed when slightly sterically hindered 2-methylbenzeneboronic acid was utilised, again requiring protodeboronation at 75 °C to furnish product **361** in 69% yield. Hetero-arylboronic acids, such as 3-pyridyl and 2-thienylboronic acids were tolerated to some extent, providing products **362** and **363** in 30% and 38% yields respectively. For these cases, the lower yields are likely due to coordination of these heterocycles to the boronic acids, hindering interception of the diazo compound, similar to when tetramethylguanidine was used as the base in optimisation studies. Utilisation of 3-thienyl (**367**) and 3-furanylboronic acids (**368**) did not result in any coupling products, even when protodeboronation was attempted at 75 °C. In addition, use of an alkylboronic acid, cyclohexylboronic acid (**369**), did not result in any observed coupling products (Figure 22).

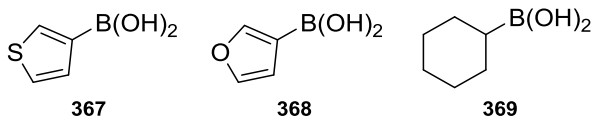
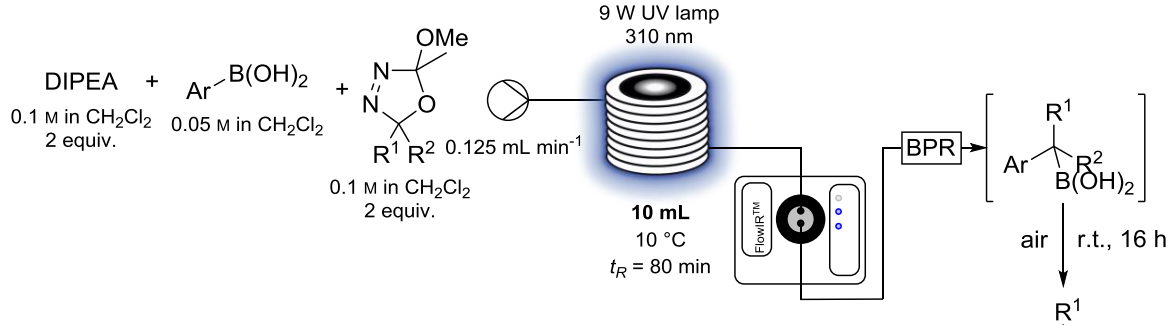
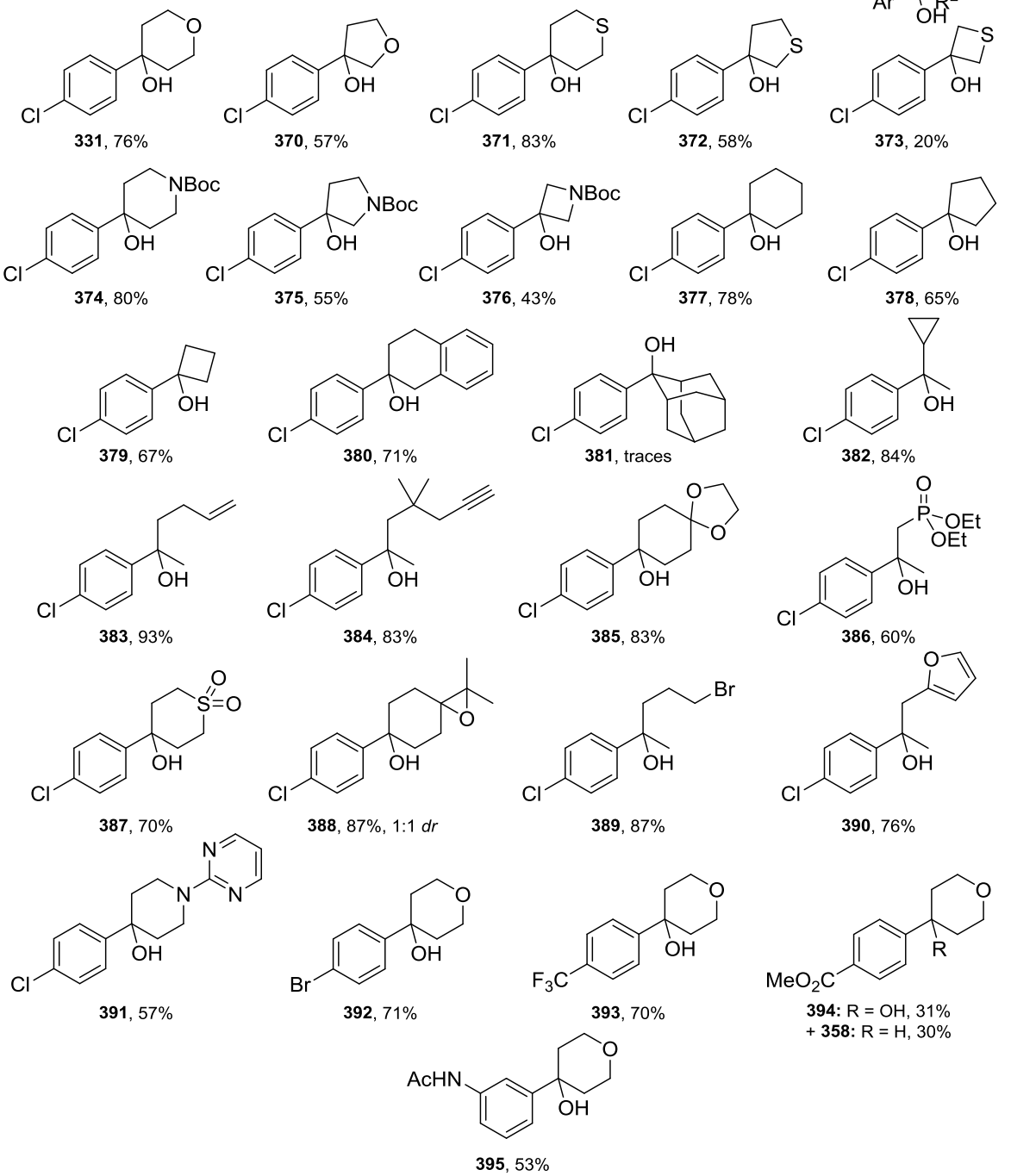


Figure 22: Unsuccessful boronic acid examples for cross-coupling.

The analogous oxidative C(sp^2)-C(sp^3) coupling processes generally proceeded in comparable yields to the protodeboronative couplings (Scheme 119). Thus, various 6-membered (**331**, **371**, **374**, **377**), 5-membered (**370**, **372**, **375**, **378**) and 4-membered rings (**373**, **376**, **379**) were tolerated, with the same observed trend in terms of higher diazo compound stability for higher sized rings. Oxidation of 4-membered substrates leading to

compounds **373** and **376** appeared to be less efficient compared to the analogous protodeboronative cases. The use of the oxadiazoline derived from 2-tetralone (**314**) proceeded analogously, providing 71% of **380**; however, oxidation of the adamantane derivative appeared to be extremely slow, only providing traces of the desired alcohol product **381**. Substrates with cyclopropyl (**382**), olefin (**383**), alkyne (**384**), acetal (**385**), phosphonate (**386**), sulfone (**387**), furan (**390**) and pyrimidine (**391**) moieties all proceeded analogously to their corresponding protodeboronative products. It is notable that the epoxide and alkyl bromide products **388** and **389** proceeded very well, both in 87% yield; no cyclised tetrahydrofuran product was observed in the latter case. In these particular two cases, the versatility of this methodology for obtaining alcohols is highlighted, since approaches utilising alternative organometallic routes would require installation of the reactive functionalities (i.e. epoxide and alkyl bromide) after the use of the Grignard/organolithium reagent. Electron-deficient (**392**, **393**) and electron-rich (**395**) arylboronic acids also performed well, with the exception of **394** where protodeboronation to form **358** appeared to be facile and only 31% of the desired oxidised product was obtained.



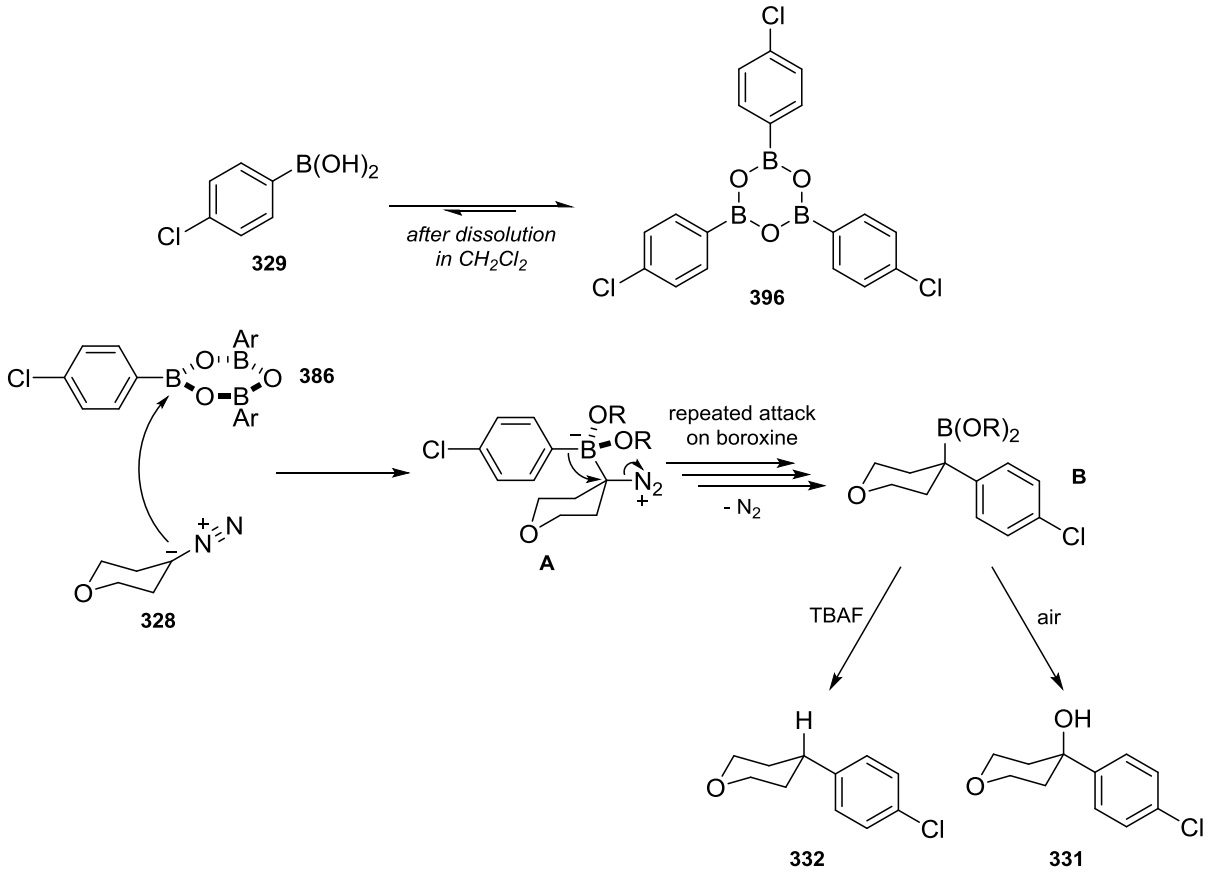


Reactions performed on 0.5 mmol scale with respect to arylboronic acid; yields stated are of isolated product.

Scheme 119: Oxidative C(sp^2)-C(sp^3) coupling using oxadiazolines and arylboronic acids.

4.3.3. Mechanistic discussion

Based on recent observations about the reactivity of boronic acid species and their derivatives,[180] it is anticipated that the mechanism of the C(sp^2)-C(sp^3) coupling process proceeds as described below (Scheme 120).



Scheme 120: Proposed mechanism for C(sp^2)-C(sp^3) coupling.

On dissolution of arylboronic acids in CH_2Cl_2, significant formation of the boroxine occurs – when 4-chlorophenylboronic acid (**329**) was analysed by ^{1}H NMR spectroscopy in CD_2Cl_2, a mixture of two different compounds were observed (Figure 23). An independent synthesis of the corresponding boroxine **396** (azeotropic removal of water by refluxing under Dean-Stark conditions) revealed that one component corresponds to the boroxine, whereas the other set of signals belongs to the boronic acid, in a 1:2.6 ratio of **329** to **396**.

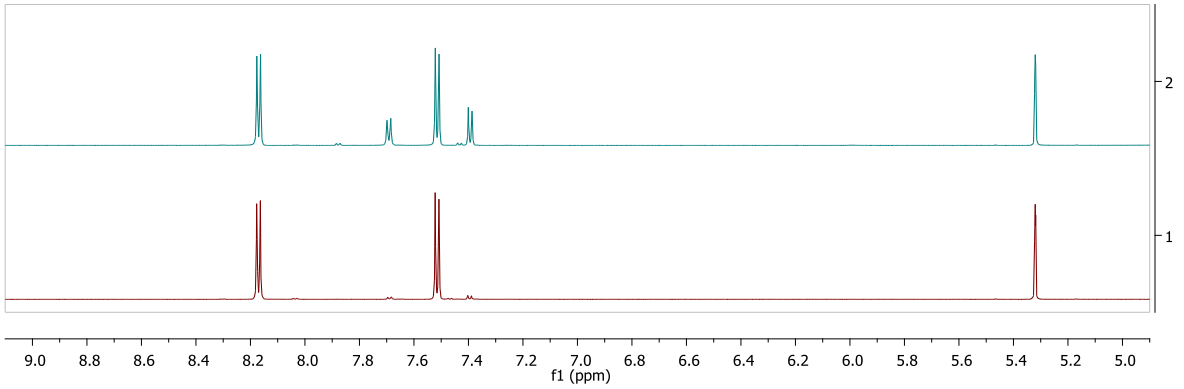
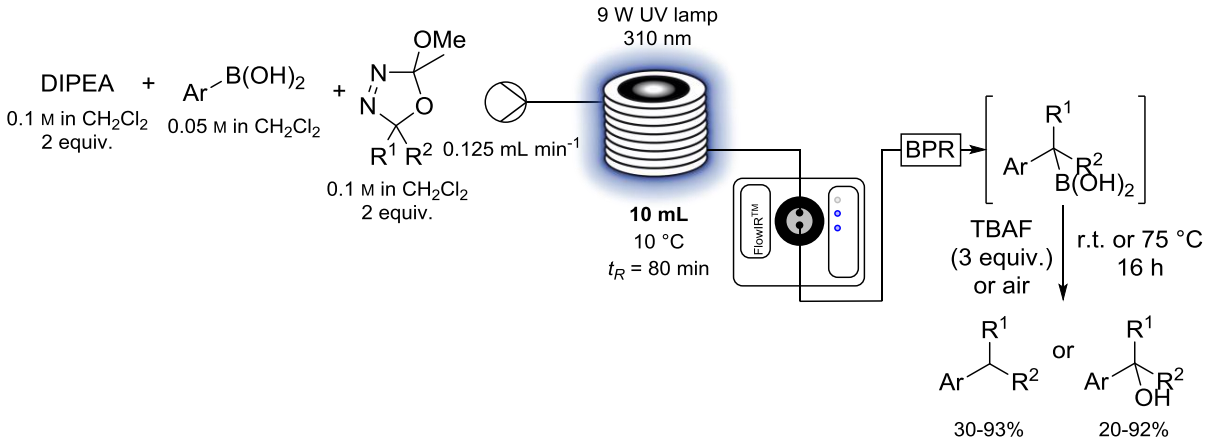


Figure 23: NMR spectra of 4-chlorophenylboronic acid (**329**) (top) and its corresponding boroxine **396** (bottom) in CD_2Cl_2.

Diazo compound **328** is generated from oxadiazoline **303** as described earlier (Section 1.2.6), which then attacks boroxine **396**, on each of the three boron atoms to give diazonium **A**. Subsequent migration of the aryl group with expulsion of nitrogen results in the organoboron derivative **B**, which then undergoes protodeboronation with TBAF or oxidation with atmospheric oxygen to provide the protodeboronated and oxidised C(sp^2)-C(sp^3) coupled products respectively.

4.4. Conclusions and outlook

To conclude, a method for the C(sp^2)-C(sp^3) coupling of non-stabilised diazo compounds, generated *in situ* by flow photolysis of oxadiazolines, and arylboronic acids was developed (Scheme 121). Changing the 'workup' conditions of the reaction allows generation of either protodeboronated C(sp^2)-C(sp^3) coupling products by treatment with TBAF, or oxidised C(sp^2)-C(sp^3) coupling products by stirring under air. A variety of 4-membered, 5-membered and 6-membered saturated heterocyclic and carbocyclic oxadiazolines were tolerated for both methods, as well as various reactive functional groups and arylboronic acids, in generally moderate to excellent yields.



Scheme 121: Summary for C(sp^2)-C(sp^3) coupling using oxadiazolines and arylboronic acids.

The functional group tolerance and scope of this newly developed process represents a major advance in metal-free C(sp^2)-C(sp^3) coupling, especially compared to the existing reports using sulfonylhydrazones as diazo precursors. An inherent limitation that comes with the use of oxadiazolines involves the inability to access alkyl aldehyde-derived diazo compound derivatives, since the required oxadiazolines for these substrates are currently inaccessible, so this represents a potential direction for further research. Nevertheless, by enabling a mild, simple route to a multitude of non-stabilised alkyl diazo compounds derived from ketones, it is anticipated that these compounds could find significant utility in organic synthesis, for example, in new cyclopropanation, cycloaddition, heteroatom-H and C-H bond insertion reactions.

5. Experimental (Appendix)

5.1. General experimental details

All batch reactions were performed using oven-dried glassware (200 °C) under an atmosphere of argon unless otherwise stated. All flow reactions were performed using a Uniqsis FlowSyn platform, a Vapourtec R2+R4 system or a Vapourtec E-series system. Solvents were freshly distilled over sodium benzophenone ketyl (THF, Et_2O) or calcium hydride (acetone, MeCN, MeOH, CH_2Cl_2, $CHCl_3$ and toluene). Additional anhydrous solvents were obtained from commercial sources and used directly (DMF, DMA, DMSO and 1,4-dioxane). DIPEA and Et_3N were freshly distilled over calcium hydride and stored over 4 Å molecular sieves. All reagents were obtained from commercial sources and used without further purification.

Flash column chromatography was performed using high-purity grade silica gel (Merck grade 9385) with a pore size 60 Å and 230–400 mesh particle size under air pressure. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} pre-coated glass backed plates and visualised by ultraviolet radiation (254 nm) and/or potassium permanganate solution as appropriate.

^{1}H NMR spectra were recorded on a 600 MHz Avance 600 BBI Spectrometer as indicated. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard ($CDCl_3$: 7.26 ppm; CD_2Cl_2: 5.32 ppm, t; DMSO-d_6: 2.50 ppm, qn; MeOD-d_4: 3.31 ppm, qn). ^{13}C NMR spectra were recorded the same spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.16 ppm, t; DMSO-d_6: 39.52 ppm, sept; MeOD-d_4: 49.00 ppm, sept). ^{19}F NMR spectra were recorded on a 376 MHz Avance III HD Spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with $CFCl_3$ as the external standard ($CFCl_3$: 0.00 ppm). ^{31}P NMR spectra were recorded on an Avance 600 BBI Spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with 85% phosphoric acid in D_2O as the external standard (H_3PO_4: 0.00 ppm). Data are reported as follows: chemical shift δ/ppm, integration (^{1}H, ^{19}F and ^{31}P), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, oct = octet, br = broad, m = multiplet or combinations thereof; ^{13}C signals are singlets unless otherwise stated), coupling constants *J* in Hz, assignment. Spectra are assigned as fully as possible, using ^{1}H-COSY, DEPT-135, HSQC, HMBC and NOESY where appropriate to facilitate structural

determination. Signals that cannot be unambiguously assigned are reported with all possible assignments separated by a slash (e.g. H1/H2) or descriptions of their environments (e.g. ArH, NH, OH). Multiple signals arising from diastereotopic or (pseudo)axial/equatorial positions are suffixed alphabetically (e.g. H1a, H1b). Overlapping signals that cannot be resolved are reported with their assignments denoted in list format (e.g. H1, H2 and H3). ^{1}H NMR signals are reported to 2 decimal places and ^{13}C signals to 1 decimal place unless rounding would produce a value identical to another signal. In this case, an additional decimal place is reported for both signals concerned.

Infrared spectra were recorded neat as thin films on a Perkin-Elmer Spectrum One FTIR spectrometer and selected peaks are reported (s = strong, m = medium, w = weak, br = broad).

High resolution mass spectrometry (HRMS) was performed using positive or negative electrospray ionisation (ESI), on either a Waters Micromass LCT Premier spectrometer or performed by the Mass Spectrometry Service for the Department of Chemistry at the University of Cambridge. All *m/z* values are reported to 4 decimal places and are within ± 5 ppm of theoretical values.

Specific optical rotation was recorded on a Perkin-Elmer Model 343 digital polarimeter, using a Na/Hal lamp set at 589 nm and with a path length of 100 mm. $[\alpha]_D$ values were measured using spectroscopy grade solvent at the specified concentration (in g/100 mL) and temperature, with units of deg 10^{-1} cm^2 g^{-1}.

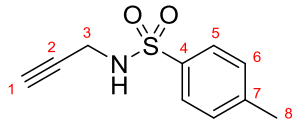
Melting points were recorded on a Stanford Research Systems OptiMelt Automated Melting Point System calibrated against vanillin (m.p. 83 °C), phenacetin (m.p. 136 °C) and caffeine (m.p. 237 °C).

Chiral HPLC analysis was conducted on an Agilent 1100 Series Chromatography system using mixtures of hexane/isopropanol as eluent on Chiralpak AS, Chiralpak OD-H, ChiralART SA or ChiralART SC columns.

X-ray crystallographic analysis was performed by Dr Andrew Bond for the Department of Chemistry at the University of Cambridge on a Bruker D8-QUEST PHOTON-100 diffractometer.

5.2. Experimental data for Chapter 2

5.2.1. Synthetic procedures and characterisation for alkyne starting materials



60

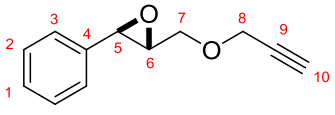
4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60): To a solution of propargylamine (3.2 mL, 50.0 mmol, 1 equiv.) in CH_2Cl_2 (125 mL) at 0 °C was added Et_3N (17.4 mL, 125.0 mmol, 2.5 equiv.) then *p*-toluenesulfonyl chloride (9.53 g, 50.0 mmol, 1 equiv.) portionwise. The mixture was stirred at r.t. for 16 h. The reaction mixture was then diluted with Et_2O (500 mL) and the organic phase washed with 1 M aqueous HCl solution (300 mL), saturated aqueous NH_4Cl solution (300 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residual precipitate was triturated with hexane (3 × 25 mL) to provide the title compound as an off-white amorphous solid (9.55 g, 45.6 mmol, 91%), m.p. 74-76 °C (lit. m.p.[181] 74-75 °C). Data are consistent with a reported example.[181]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2 H, H5), 7.31 (d, *J* = 8.2 Hz, 2 H, H6), 4.82 (br t, *J* = 5.8 Hz, 1 H, NH), 3.82 (dd, *J* = 5.8, 2.5 Hz, 2 H, H3), 2.43 (s, 3 H, H8), 2.10 (t, *J* = 2.5 Hz, 1 H, H1).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.0 (C7), 136.6 (C4), 129.8 (C6), 127.5 (C5), 78.1 (C2), 73.1 (C1), 33.0 (C3), 21.7 (C8).

FTIR (ν_{max}, cm^{-1}): 3276 (m, NH and alkyne CH), 1598 (w), 1495 (w), 1428 (w), 1324 (m), 1307 (m), 1292 (w), 1186 (w), 1156 (s), 1121 (w), 1093 (m), 1070 (m), 1019 (w), 993 (w), 925 (w), 813 (m).

HRMS (ESI): calculated for $C_{10}H_{12}NO_2S$ $[M+H]^+$ 210.0583, found 210.0586.



(2*RS*,3*RS*)-2-Phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane: To a suspension of sodium hydride (88 mg, 2.40 mmol, 1.2 equiv., 60% dispersion in mineral oil) in anhydrous THF (5 mL) was added a solution of *trans*-3-phenylglycidol (300 mg, 2.00 mmol, 1.0 equiv.) in anhydrous THF (5 mL) slowly dropwise at 0 °C under an argon atmosphere. The mixture was

stirred further at this temperature for 10 min. Propargyl bromide (0.18 mL, 2.40 mmol, 1.2 equiv.) was then added slowly dropwise at 0 °C and the mixture stirred further at r.t. for 1 h. The reaction mixture was quenched with a few drops of EtOAc and the solvent removed under reduced pressure. EtOAc (25 mL) was added to the residue and the organic layer washed with water (2 × 25 mL), brine (25 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) to provide the title compound as a colourless oil (350 mg, 1.86 mmol, 93%). Data are consistent with a reported example.[182]

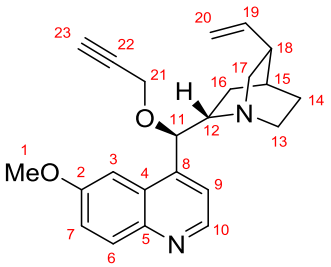
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2 H, H2), 7.33 – 7.29 (m, 1 H, H1), 7.29 – 7.26 (m, 2 H, H3), 4.26 (d, *J* = 2.4 Hz, 2 H, H8), 3.92 (dd, *J* = 11.4, 3.1 Hz, 1 H, H7a), 3.82 (dd, *J* = 6.3, 2.1 Hz, 1 H, H5), 3.70 (dd, *J* = 11.4, 5.3 Hz, 1 H, H7b), 3.24 (ddd, *J* = 5.3, 3.1, 2.1 Hz, 1 H, H6), 2.47 (t, *J* = 2.4 Hz, 1 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 136.7 (C4), 128.6 (C2), 128.5 (C1), 125.8 (C3), 79.3 (C9), 75.2 (C10), 69.4 (C7), 60.9 (C6), 58.7 (C8), 56.0 (C5).

FTIR (ν_{max}, cm^{-1}): 3289 (w, alkyne CH), 2859 (w), 2118 (w, C≡C), 1743 (w), 1605 (w), 1498 (w), 1462 (w), 1443 (w), 1359 (w), 1243 (w), 1202 (w), 1097 (s), 1027 (w), 976 (w), 932 (w), 910 (w), 879 (m), 838 (w).

HRMS (ESI): calculated for $C_{12}H_{12}O_2Na$ $[M+Na]^+$ 211.0730, found 211.0731.

***R*$_f$** = 0.25 (10% EtOAc/hexane).



(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-Methoxyquinolin-4-yl)(prop-2-yn-1-yloxy)methyl)-5-vinyl-quinuclidine: To a suspension of sodium hydride (0.40 g, 10.0 mmol, 2.0 equiv., 60% dispersion in mineral oil) in anhydrous DMF (15 mL) was added a solution of quinine (1.62 g, 5.0 mmol, 1.0 equiv.) in anhydrous DMF (15 mL) slowly dropwise at 0 °C under an argon atmosphere. The mixture was stirred further at this temperature for 10 min. Propargyl bromide (0.52 mL, 6.0 mmol, 1.2 equiv.) was then added slowly dropwise at 0 °C and the mixture stirred further at r.t. for 3 h. The reaction mixture was quenched with water (50 mL)

and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with water (4 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 60% EtOAc/38% hexane/2% Et_3N) to provide the title compound as an off-white amorphous solid (1.63 g, 4.5 mmol, 90%), m.p. 87-89 °C (lit. m.p.[183] 88-90 °C). Data are consistent with a reported example.[183]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.4 Hz, 1 H, H10), 8.03 (t, *J* = 5.9 Hz, 1 H, H6), 7.41 (d, *J* = 4.4 Hz, 1 H, H9), 7.39 – 7.34 (m, 2 H, H3 and H7), 5.83 – 5.68 (m, 1 H, H19), 5.31 (br s, 1 H, H11), 4.95 (dt, *J* = 17.1, 1.4 Hz, 1 H, $H20_{trans}$), 4.91 (dt, *J* = 10.3, 1.4 Hz, 1 H, $H20_{cis}$), 4.21 (dd, *J* = 15.9, 2.4 Hz, 1 H, H21a), 3.93 (s, 3 H, H1), 3.89 (dd, *J* = 15.9, 2.4 Hz, 1 H, H21b), 3.41 (br s, 1 H, H13a), 3.15 (br s, 1 H, H12), 3.07 (dd, *J* = 13.8, 10.1 Hz, 1 H, H17a), 2.72 – 2.62 (m, 1 H, H13b), 2.62 – 2.55 (m, 1 H, H17b), 2.45 (t, *J* = 2.4 Hz, 1 H, H23), 2.25 (br s, 1 H, H18), 1.82 – 1.79 (m, 1 H, H15), 1.79 – 1.71 (m, 2 H, H14a and H16a), 1.67 (br s, 1 H, H16b), 1.56 – 1.48 (m, 1 H, H14b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.9 (C2), 147.7 (C10), 144.8 (C8), 143.9 (C5), 142.1 (C19), 132.0 (C6), 127.6 (C4), 121.9 (C7), 120.0 – 118.0 (br, C9), 114.3 (C20), 101.5 – 101.0 (br, C3), 79.4 (C22), 77.5 –76.7 (br, obscured by $CDCl_3$ peak, C11), 75.1 (C23), 60.1 (C12), 57.3 (C17), 56.3 (C21), 55.8 (C1), 43.2 (C13), 40.2 (C18), 27.87 (C14/C15), 27.86 (C14/C15), 23.5 – 22.5 (br, C16).

FTIR (ν_{max}, cm^{-1}): 2935 (m), 2099 (w, C≡C), 1620 (m), 1591 (w), 1506 (m), 1473 (m), 1455 (m), 1429 (m), 1362 (m), 1306 (w), 1240 (s), 1228 (s), 1107 (m), 1082 (s), 1050 (s), 1032 (s), 905 (m), 852 (m), 839 (m), 817 (s).

HRMS (ESI): calculated for $C_{23}H_{27}N_2O_2Na$ $[M+H]^+$ 363.2067, found 363.2077.

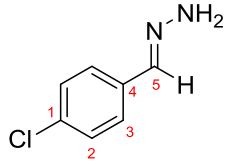
$\boldsymbol{R_f}$ = 0.20 (60% EtOAc/38% hexane/2% Et_3N).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -161.5 ($CHCl_3$, *c* = 1.0).

5.2.2. Synthetic procedures and characterisation for hydrazone starting materials

General procedure for aldehyde-derived hydrazone formation: To a solution of aldehyde (20.0 mmol, 1.0 equiv.) in methanol (20 mL) was added hydrazine hydrate (1.2 mL, 24 mmol, 1.2 equiv.) and the mixture stirred at r.t. for 1 h. The mixture was then evaporated under reduced pressure to provide the desired hydrazone. The crude hydrazone was used for generation of the corresponding diazo compound without further purification.

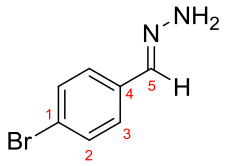
General procedure for ketone-derived hydrazone formation: To a solution of ketone (20.0 mmol, 1.0 equiv.) in methanol (20 mL) was added hydrazine hydrate (2.9 mL, 60.0 mmol, 3.0 equiv.) and the mixture stirred at 80 °C for 3 h in a sealed vial. The solvent was removed under reduced pressure and the residue diluted with water (25 mL) and CH_2Cl_2 (25 mL). The mixture was separated, the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to provide the desired hydrazone. The crude hydrazone was used for generation of the corresponding diazo compound without further purification.



62

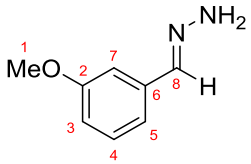
(4-Chlorobenzylidene)hydrazine (62): Following the general procedure for aldehyde-derived hydrazone formation using 4-chlorobenzaldehyde (2.81 g, 20.0 mmol), provided the title compound as a white crystalline solid (3.08 g, 19.9 mmol, 99%), m.p. 59-61 °C (lit. m.p.[184] 60-61 °C). Data are consistent with a reported example.[185]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (s, 1 H, H5), 7.47 (d, *J* = 8.5 Hz, 2 H, H3), 7.31 (d, *J* = 8.5 Hz, 2 H, H2), 5.54 (br s, 2 H, NH).
^{13}C NMR (150 MHz, $CDCl_3$): δ 141.8 (C5), 134.4 (C4), 133.7 (C1), 128.9 (C2), 127.4 (C3).
FTIR (ν_{max}, cm^{-1}): 3357 (w, NH_2), 3186 (w, NH_2), 1625 (w), 1594 (w), 1486 (w), 1393 (w), 1249 (w), 1218 (w), 1109 (w), 1090 (m), 1010 (w), 961 (w), 924 (w), 912 (w), 864 (w), 824 (s).
HRMS (ESI): calculated for $C_7H_7N_2ClNa$ $[M+Na]^+$ 177.0190, found 177.0188.



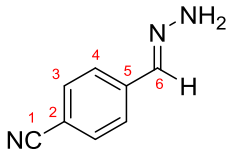
(4-Bromobenzylidene)hydrazine: Following the general procedure for aldehyde-derived hydrazone formation using 4-bromobenzaldehyde (3.70 g, 20.0 mmol), provided the title compound as an off-white crystalline solid (3.98 g, 19.9 mmol, 99%), m.p. 73-75 °C (lit. m.p.[184] 77-78 °C). Data are consistent with a reported example.[184]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (s, 1 H, H5), 7.47 (d, *J* = 8.5 Hz, 2 H, H2), 7.41 (d, *J* = 8.5 Hz, 2 H, H3), 5.56 (br s, 2 H, NH).
^{13}C NMR (150 MHz, $CDCl_3$): δ 141.7 (C5), 134.3 (C4), 131.9 (C2), 127.7 (C3), 122.6 (C1).
FTIR (ν_{max}, cm^{-1}): 3353 (w, NH_2), 3194 (w, NH_2), 1627 (w), 1586 (m), 1483 (w), 1391 (m), 1069 (s), 1006 (m), 924 (m), 912 (m), 862 (m), 818 (s).
HRMS (ESI): calculated for $C_7H_7N_2BrNa$ $[M+Na]^+$ 220.9685, found 220.9690.



(3-Methoxybenzylidene)hydrazine: Following the general procedure for aldehyde-derived hydrazone formation using *m*-anisaldehyde (2.72 g, 20.0 mmol), provided the title compound as a yellow oil (2.99 g, 19.9 mmol, 99%). Data are consistent with a reported example.[186]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (s, 1 H, H8), 7.26 (t, *J* = 7.9 Hz, 1 H, H4), 7.16 (dd, *J* = 2.5, 0.8 Hz, 1 H, H7), 7.07 (dt, *J* = 7.9, 0.8 Hz, 1 H, H5), 6.86 (ddd, *J* = 7.9, 2.5, 0.8 Hz, 1 H, H3), 5.51 (br s, 2 H, NH), 3.83 (s, 3 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 160.0 (C2), 143.1 (C8), 136.7 (C6), 129.7 (C4), 119.5 (C5), 115.4 (C3), 110.2 (C7), 55.4 (C1).
FTIR (ν_{max}, cm^{-1}): 3387 (w, NH_2), 3200 (w, NH_2), 2911 (w), 2835 (w), 1597 (s), 1575 (s), 1489 (m), 1466 (m), 1455 (m), 1431 (m), 1397 (w), 1317 (w), 1288 (m), 1263 (s), 1195 (w), 1155 (s), 1072 (w), 1038 (s), 994 (w), 967 (w), 922 (m), 862 (w).
HRMS (ESI): calculated for $C_8H_{10}N_2ONa$ $[M+Na]^+$ 173.0685, found 173.0692.



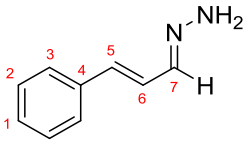
4-(Hydrazonomethyl)benzonitrile: Following the general procedure for aldehyde-derived hydrazone formation using 4-formylbenzonitrile (2.62 g, 20.0 mmol) provided the title compound as a yellow amorphous solid (2.90 g, 20.0 mmol, 99%), m.p. 63-66 °C (lit. m.p.[187] 64-66 °C). Data are consistent with a reported example.[188]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (s, 1 H, H6), 7.62 (s, 4 H, H3 and H4), 5.81 (br s, 2 H, NH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 139.9 (C6), 139.7 (C5), 132.5 (C3), 126.5 (C4), 119.1 (C1), 111.5 (C2).

FTIR (ν_{max}, cm^{-1}): 3377 (w, NH_2), 3198 (w, NH_2), 2221 (m, C≡N), 1589 (s), 1552 (m), 1503 (m), 1398 (m), 1244 (w), 1175 (w), 1091 (w), 909 (s), 869 (w), 824 (s).

HRMS (ESI): calculated for $C_8H_7N_3Na$ $[M+Na]^+$ 168.0532, found 168.0530.



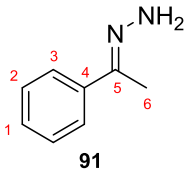
((*E*)-3-Phenylallylidene)hydrazine: Following the general procedure for aldehyde-derived hydrazone formation using *trans*-cinnamaldehyde (2.64 g, 20.0 mmol) provided the title compound as a yellow waxy solid (2.91 g, 19.9 mmol, 99%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.1 Hz, 1 H, H7), 7.42 (d, *J* = 7.5 Hz, 2 H, H3), 7.33 (t, *J* = 7.5 Hz, 2 H, H2), 7.28 – 7.24 (m, 1 H, H1), 6.86 (dd, *J* = 16.1, 9.1 Hz, 1 H, H6), 6.66 (d, *J* = 16.1 Hz, 1 H, H5), 4.88 (br s, 2 H, NH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.3 (C7), 136.6 (C4), 134.9 (C5), 128.8 (C2), 128.3 (C1), 126.7 (C3), 125.9 (C6).

FTIR (ν_{max}, cm^{-1}): 3322 (w, NH_2), 3177 (w, NH_2), 3025 (w), 2907 (w), 1640 (w), 1578 (w), 1485 (w), 1447 (m), 1383 (w), 1292 (w), 1257 (w), 1208 (w), 1178 (w), 1151 (w), 1127 (w), 1088 (m), 971 (s), 933 (w), 915 (w), 842 (w).

HRMS (ESI): calculated for $C_9H_{10}N_2Na$ $[M+Na]^+$ 169.0736, found 168.0735.



91

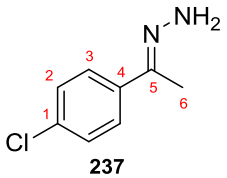
(1-Phenylethylidene)hydrazine (91): Following the general procedure for ketone-derived hydrazone formation using acetophenone (2.40 g, 20.0 mmol) provided the title compound as a yellow oil (2.00 g, 14.9 mmol, 75%). Data are consistent with a reported example.[185]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 – 7.63 (m, 2 H, H3), 7.38 – 7.33 (m, 2 H, H2), 7.32 – 7.28 (m, 1 H, H1), 5.36 (br s, 2 H, NH_2), 2.13 (s, 3 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.4 (C5), 139.5 (C4), 128.4 (C2), 128.1 (C1), 125.6 (C3), 11.7 (C6).

FTIR (ν_{max}, cm^{-1}): 3385 (w, NH_2), 3214 (w, NH_2), 1592 (s), 1571 (w), 1495 (s), 1444 (s), 1369 (s), 1330 (w), 1254 (w), 1115 (m), 1079 (m), 1064 (m), 1026 (s), 951 (w), 914 (w).

HRMS (ESI): calculated for $C_8H_{10}N_2Na$ $[M+Na]^+$ 157.0736, found 157.0740.



237

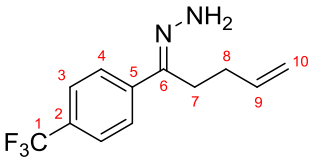
(1-(4-Chlorophenyl)ethylidene)hydrazine (237): Following the general procedure for ketone-derived hydrazone formation using 4'-chloroacetophenone (3.09 g, 20.0 mmol) provided the title compound as an off-white crystalline solid (3.40 g, 20.0 mmol, 99%), m.p. 48.5-49.5 °C (lit. m.p.[189] 48.4-50.1 °C). Data are consistent with a reported example.[185]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.6 Hz, 2 H, H3), 7.30 (d, *J* = 8.6 Hz, 2 H, H2), 5.38 (br s, 2 H, NH_2), 2.09 (s, 3 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.0 (C5), 137.9 (C4), 133.9 (C1), 128.5 (C2), 126.8 (C3), 11.5 (C6).

FTIR (ν_{max}, cm^{-1}): 3356 (w, NH_2), 3215 (w, NH_2), 1638 (w), 1599 (w), 1488 (m), 1395 (w), 1369 (w), 1333 (w), 1270 (w), 1108 (w), 1092 (s), 1007 (m), 958 (w), 822 (s).

HRMS (ESI): calculated for $C_8H_9N_2ClNa$ $[M+Na]^+$ 191.0346, found 191.0340.



(1-(4-(Trifluoromethyl)phenyl)pent-4-en-1-ylidene)hydrazine: Following the general procedure for ketone-derived hydrazone formation using 1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (4.56 g, 20.0 mmol) provided the title compound as a yellow waxy solid (4.24 g, 17.5 mmol, 88%).

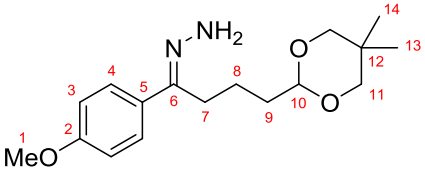
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2 H, H4), 7.58 (d, *J* = 8.2 Hz, 2 H, H3), 5.86 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H, H9), 5.61 (br s, 2 H, NH_2), 5.11 (dq, *J* = 17.0, 1.4 Hz, 1 H, $H10_{trans}$), 5.05 (dd, *J* = 10.2, 1.4 Hz, 1 H, $H10_{cis}$), 2.74 – 2.68 (m, 2 H, H7), 2.33 – 2.27 (m, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 148.0 (q, *J* = 0.5 Hz, C6), 141.8 (q, *J* = 1.3 Hz, C5), 136.9 (C9), 129.8 (q, *J* = 32.4 Hz, C2), 125.8 (C4), 125.4 (q, *J* = 3.9 Hz, C3), 124.3 (q, *J* = 271.8 Hz, C1), 116.2 (C10), 29.2 (C8), 24.6 (C7).

^{19}F NMR (376 MHz, $CDCl_3$): -62.5 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 3311 (w, NH_2), 3210 (w, NH_2), 1630 (w), 1524 (w), 1502 (w), 1408 (w), 1323 (s), 1161 (m), 1108 (s), 1067 (s), 1016 (m), 980 (w), 956 (w), 918 (w), 857 (m), 846 (m).

HRMS (ESI): calculated for $C_{12}H_{13}F_3N_2Na$ $[M+Na]^+$ 265.0923, found 265.0926.



(4-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-(4-methoxyphenyl)butylidene)hydrazine: Following the general procedure for ketone-derived hydrazone formation using 4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-methoxyphenyl)butan-1-one (1.46 g, 5.00 mmol) provided the title compound as a yellow viscous oil (1.53 g, 4.99 mmol, 99%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 9.0 Hz, 2 H, H4), 6.85 (d, *J* = 9.0 Hz, 2 H, H3), 5.40 (br s, 2 H, NH_2), 4.46 (t, *J* = 4.8 Hz, 1 H, H10), 3.80 (s, 3 H, H1), 3.59 (d, *J* = 11.2 Hz, 2 H, H11a), 3.40 (d, *J* = 11.2 Hz, 2 H, H11b), 2.66 – 2.59 (m, 2 H, H7), 1.75 – 1.64 (m, 4 H, H8 and H9), 1.17 (s, 3 H, H13/H14), 0.70 (s, 3 H, H13/H14).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.7 (C2), 150.7 (C6), 131.3 (C5), 127.0 (C4), 113.8 (C3), 101.9 (C10), 77.3 (C11), 55.4 (C1), 34.4 (C9), 30.3 (C12), 25.3 (C7), 23.1 (C13/C14), 21.9 (C13/C14), 20.0 (C8).

FTIR (ν_{max}, cm^{-1}): 3401 (w, NH_2), 3220 (w, NH_2), 2955 (w), 2839 (w), 1675 (w), 1603 (m), 1511 (s), 1464 (m), 1394 (m), 1363 (w), 1307 (m), 1247 (s), 1174 (m), 1131 (s), 1096 (m), 1033 (m), 1014 (m), 969 (w), 910 (m), 833 (m), 808 (w).

HRMS (ESI): calculated for $C_{17}H_{26}N_2O_3Na$ $[M+Na]^+$ 329.1836, found 329.1842.

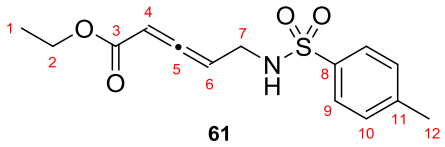
5.2.3. Synthetic procedures and characterisation for allenes

General procedure for allene formation with aldehyde-derived hydrazones: *Conditioning phase:* A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through a column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1} for 20 min and the reactor output was monitored using a FlowIR® device. The flow was switched to solvent (DIPEA, 0.2 M in CH_2Cl_2) for 10 min. The column was then ready for the generation of the diazo compound.

Generation phase: A vial was charged with the appropriate alkyne (0.2 mmol, 1.0 equiv.), copper(I) iodide (3.9 mg, 0.02 mmol, 0.1 equiv.), 1,4-dioxane (2 mL) and Et_3N (0.05 mL, 0.4 mmol, 2 equiv.) and pre-mixed for 10 min. A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through the pre-conditioned column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak was stable, 3 mL of the output (1.5 equiv. with respect to the hydrazone) was directly added into the reaction vial (over 6 min) containing the copper acetylide and the reaction mixture further stirred at r.t. for 10 min. The mixture was then filtered through a pad of Celite, eluting with EtOAc, and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography to provide the desired disubstituted allene product. Any excess diazo compound produced during the conditioning phase or the generation phase before steady-state was reached was gently quenched by directing the output of the flow reactor into a stirred suspension of copper(I) iodide (0.10 g) in MeOH (25 mL).

General procedure for allene formation with ketone-derived hydrazones: (N.B. Diazo compound generation from ketone-derived hydrazones does not require a pre-conditioning phase for the MnO_2 column reactor). A vial was charged with the appropriate alkyne (0.2 mmol, 1.0 equiv.), copper(I) iodide (3.9 mg, 0.02 mmol, 0.1 equiv.), 2,6-lutidine (4.6 µL, 0.04 mmol, 0.2 equiv.), 1,4-dioxane (2 mL), Et_3N (0.05 mL, 0.4 mmol, 2 equiv.) and pre-mixed for 10 min. A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through the column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak was stable, 3 mL of the output (1.5 equiv. with respect to the hydrazone) was directly added into the reaction vial (over 6 min) containing the copper

acetylide and the reaction mixture further stirred at r.t. for 10 min. The mixture was then filtered through a pad of Celite, eluting with EtOAc, and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography to provide the desired trisubstituted allene product. Any excess diazo compound produced during the generation phase before steady-state was reached was gently quenched by directing the output of the flow reactor into a stirred suspension of copper(I) iodide (0.10 g) in MeOH (25 mL).



61

Ethyl 5-((4-methylphenyl)sulfonamido)penta-2,3-dienoate (61): A vial was charged with 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol, 1.0 equiv.), copper(I) iodide (3.9 mg, 0.02 mmol, 0.1 equiv.), 1,4-dioxane (2 mL) and Et_3N (0.05 mL, 0.4 mmol, 2 equiv.) and pre-mixed for 10 min. To this reaction mixture was added a solution of ethyl diazoacetate (**39**) (0.03 mL, 0.3 mmol, 1.5 equiv.) in dioxane (1 mL) slowly dropwise over 10 min and stirred at r.t. for 16 h. The mixture was then filtered through a pad of Celite, eluting with EtOAc, and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) to provide the title compound as a yellow gum (49.5 mg, 0.168 mmol, 84%).

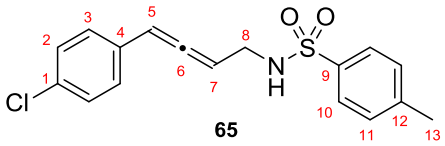
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2 H, H9), 7.31 (d, *J* = 8.2 Hz, 2 H, H10), 5.62 (dt, *J* = 6.1, 2.9 Hz, 1 H, H6), 5.56 (q, *J* = 6.1 Hz, 1 H, H4), 4.74 (br t, *J* = 6.2 Hz, 1 H, NH), 4.21 – 4.14 (m, 2 H, H2), 3.78 – 3.66 (m, 2 H, H7), 2.43 (s, 3 H, H12), 1.27 (t, *J* = 7.1 Hz, 3 H, H1).

^{13}C NMR (150 MHz, $CDCl_3$): δ 211.7 (C5), 165.2 (C3), 143.9 (C11), 137.0 (C8), 129.9 (C10), 127.3 (C9), 93.0 (C4), 91.1 (C6), 61.4 (C2), 40.8 (C7), 21.7 (C12), 14.3 (C1).

FTIR (ν_{max}, cm^{-1}): 3270 (br w, NH), 2982 (w), 1966 (w, C=C=C), 1714 (m, C=O), 1598 (w), 1495 (w), 1424 (w), 1367 (w), 1330 (m), 1277 (w), 1158 (s), 1094 (m), 1034 (w), 870 (w), 815 (w).

HRMS (ESI): calculated for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$ 318.0770, found 318.0781.

R_f = 0.28 (30% EtOAc/hexane).



65

***N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (65):** Following the general procedure for allene formation with aldehyde-derived hydrazones using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as an off-white amorphous solid (62.3 mg, 0.187 mmol, 93%), m.p. 88-90 °C.

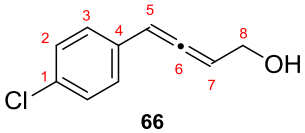
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2 H, H10), 7.25 (d, *J* = 8.2 Hz, 2 H, H11), 7.21 (d, *J* = 8.5 Hz, 2 H, H2), 7.11 (d, *J* = 8.5 Hz, 2 H, H3), 6.15 (dt, *J* = 6.2, 3.2 Hz, 1 H, H5), 5.52 (q, *J* = 6.2 Hz, 1 H, H7), 5.10 (t, *J* = 6.0 Hz, 1 H, NH), 3.73 – 3.68 (m, 2 H, H8), 2.40 (s, 3 H, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9 (C6), 143.7 (C12), 137.0 (C9), 133.1 (C1), 132.0 (C4), 129.8 (C11), 128.9 (C2), 128.2 (C3), 127.2 (C10), 96.9 (C5), 92.5 (C7), 41.7 (C8), 21.6 (C13).

FTIR (ν_{max}, cm^{-1}): 3276 (w, NH), 2924 (w), 1957 (w, C=C=C), 1723 (w), 1597 (w), 1491 (m), 1408 (w), 1323 (m), 1265 (w), 1155 (s), 1090 (s), 1013 (m), 874 (m), 834 (m), 812 (s).

HRMS (ESI): calculated for $C_{17}H_{16}NO_2SClNa$ $[M+Na]^+$ 356.0482, found 356.0477.

***R*$_f$** = 0.24 (20% EtOAc/hexane).



66

4-(4-Chlorophenyl)buta-2,3-dien-1-ol (66): Following the general procedure for allene formation with aldehyde-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a colourless oil (33.0 mg, 0.183 mmol, 91%).

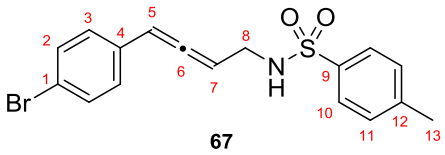
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2 H, H2), 7.23 (d, *J* = 8.6 Hz, 2 H, H3), 6.29 (dt, *J* = 6.0, 2.9 Hz, 1 H, H5), 5.80 (q, *J* = 6.0 Hz, 1 H, H7), 4.27 (br s, 2 H, H8), 1.80 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.4 (C6), 132.9 (C1), 132.4 (C4), 128.9 (C2), 128.1 (C3), 96.4 (C5), 96.3 (C7), 60.3 (C8).

FTIR (ν_{max}, cm^{-1}): 3330 (br m, OH), 2872 (w), 1951 (m, C=C=C), 1490 (s), 1428 (m), 1390 (m), 1352 (m), 1260 (w), 1198 (w), 1089 (s), 1012 (s), 872 (s), 830 (s).

HRMS (ESI): calculated for $C_{10}H_{10}OCl$ $[M+H]^+$ 181.0415, found 181.0411.

***R*$_f$** = 0.31 (20% EtOAc/hexane).



67

***N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (67):** Following the general procedure for allene formation with aldehyde-derived hydrazones using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) and trituration with Et_2O provided the title compound as an off-white amorphous solid (69.9 mg, 0.185 mmol, 92%), m.p. 122-124 °C (lit. m.p.[190] 120-123 °C). Data are consistent with a reported example.[190]

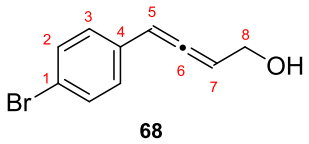
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2 H, H10), 7.39 (d, *J* = 8.4 Hz, 2 H, H2), 7.27 (d, *J* = 8.2 Hz, 2 H, H11), 7.05 (d, *J* = 8.4 Hz, 2 H, H3), 6.15 (dt, *J* = 6.0, 3.1 Hz, 1 H, H5), 5.53 (q, *J* = 6.0 Hz, 1 H, H7), 4.69 (t, *J* = 5.7 Hz, 1 H, NH), 3.73 – 3.67 (m, 2 H, H8), 2.42 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.9 (C6), 143.8 (C9), 137.0 (C12), 132.4 (C1), 131.9 (C2), 129.9 (C11), 128.6 (C3), 127.3 (C10), 121.4 (C4), 97.2 (C5), 92.7 (C7), 41.6 (C8), 21.7 (C13).

FTIR (ν_{max}, cm^{-1}): 3229 (m, NH), 1948 (w, C=C=C), 1597 (w), 1486 (m), 1454 (m), 1423 (m), 1346 (m), 1318 (m), 1305 (m), 1289 (m), 1235 (w), 1155 (s), 1124 (m), 1089 (m), 1067 (m), 1058 (m), 1008 (m), 916 (m), 877 (m), 828 (m), 817 (s), 809 (m).

HRMS (ESI): calculated for $C_{17}H_{17}NO_2SBr$ $[M+H]^+$ 378.0158, found 378.0150.

***R*$_f$** = 0.31 (25% EtOAc/hexane).



68

4-(4-Bromophenyl)buta-2,3-dien-1-ol (68): Following the general procedure for allene formation with aldehyde-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a colourless oil (44.9 mg, 0.199 mmol, 99%). Data are consistent with a reported example.[120]

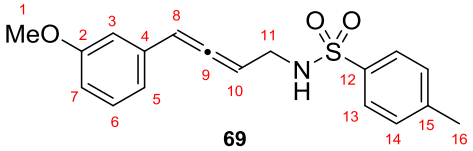
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.16 (d, *J* = 8.4 Hz, 2 H, H3), 6.25 (dt, *J* = 6.0, 2.9 Hz, 1 H, H5), 5.77 (q, *J* = 6.0 Hz, 1 H, H7), 4.25 (br s, 2 H, H8), 1.84 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.5 (C6), 133.0 (C1), 131.9 (C2), 128.5 (C3), 121.0 (C4), 96.44 (C5/C7), 96.37 (C5/C7), 60.3 (C8).

FTIR (ν_{max}, cm^{-1}): 3344 (br m, OH), 2876 (w), 1950 (m, C=C=C), 1698 (m), 1588 (m), 1488 (s), 1428 (m), 1388 (m), 1264 (m), 1204 (m), 1175 (m), 1103 (m), 1069 (s), 1041 (m), 1008 (s), 873 (m), 828 (s).

HRMS (ESI): calculated for $C_{10}H_{10}OBr$ $[M+H]^+$ 224.9910, found 224.9901.

***R*$_f$** = 0.27 (25% EtOAc/hexane).



69

***N*-(4-(3-Methoxyphenyl)buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (69):** Following the general procedure for allene formation with aldehyde-derived hydrazones using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol) and (3-methoxybenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a colourless oil (53.5 mg, 0.162 mmol, 81%).

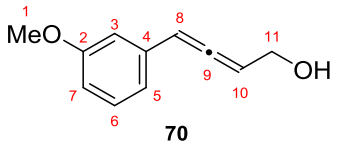
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2 H, H13), 7.28 (d, *J* = 8.2 Hz, 2 H, H14), 7.21 (t, *J* = 7.8 Hz, 1 H, H6), 6.81 (d, *J* = 7.8 Hz, 1 H, H7), 6.79 – 6.76 (m, 2 H, H3 and H5), 6.18 (dt, *J* = 6.0, 3.0 Hz, 1 H, H8), 5.53 (q, *J* = 6.0 Hz, 1 H, H10), 4.96 (t, *J* = 6.0 Hz, 1 H, NH), 3.80 (s, 3 H, H1), 3.69 (td, *J* = 6.0, 3.0 Hz, 2 H, H11), 2.42 (s, 3 H, H16).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.8 (C9), 159.9 (C2), 143.6 (C12), 136.8 (C15), 134.7 (C4), 129.8 (C14), 129.7 (C6), 127.2 (C13), 119.7 (C7), 113.2 (C5), 112.2 (C3), 97.8 (C8), 92.1 (C10), 55.3 (C1), 41.7 (C11), 21.6 (C16).

FTIR (ν_{max}, cm^{-1}): 3275 (w, NH), 1954 (w, C=C=C), 1598 (m), 1490 (m), 1454 (m), 1438 (m), 1321 (m), 1291 (m), 1265 (m), 1153 (s), 1092 (m), 1040 (m), 876 (m), 836 (m), 813 (m).

HRMS (ESI): calculated for $C_{18}H_{19}NO_3SNa$ $[M+Na]^+$ 352.0978, found 352.0961.

***R*$_f$** = 0.24 (25% EtOAc/hexane).



70

4-(3-Methoxyphenyl)buta-2,3-dien-1-ol (70): Following the general procedure for allene formation with aldehyde-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and (3-methoxybenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 25% EtOAc/hexane), provided the title compound as a colourless oil (32.6 mg, 0.185 mmol, 93%). Data are consistent with a reported example.[191]

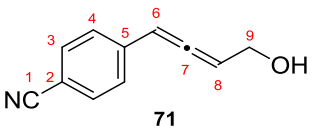
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.9 Hz, 1 H, H6), 6.90 (d, *J* = 7.9 Hz, 1 H, H7), 6.85 (m, 1 H, H3), 6.77 (dd, *J* = 8.9, 2.4 Hz, 1 H, H5), 6.29 (dt, *J* = 6.0, 2.9 Hz, 1 H, H8), 5.78 (q, *J* = 6.0 Hz, 1 H, H10), 4.25 (br s, 2 H, H11), 3.80 (s, 3 H, H1), 1.94 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.4 (C9), 159.9 (C2), 135.3 (C4), 129.7 (C6), 119.5 (C7), 112.9 (C5), 112.2 (C3), 97.2 (C8), 96.0 (C10), 60.4 (C11), 55.3 (C1).

FTIR (ν_{max}, cm^{-1}): 3360 (br m, OH), 2940 (m), 2836 (w), 1950 (m, C=C=C), 1598 (s), 1584 (s), 1490 (s), 1466 (s), 1438 (m), 1408 (m), 1317 (m), 1265 (s), 1154 (s), 1111 (w), 1041 (s), 1011 (m), 875 (m).

HRMS (ESI): calculated for $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 199.0730, found 199.0720.

***R*$_f$** = 0.20 (25% EtOAc/hexane).

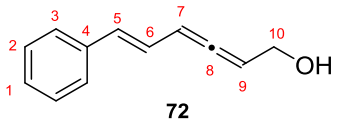


71

4-(4-Hydroxybuta-1,2-dien-1-yl)benzonitrile (71): Following the general procedure for allene formation with aldehyde-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and 4-(hydrazonomethyl)benzonitrile, purified by silica gel column

chromatography (eluent: 35% EtOAc/hexane) provided the title compound as a colourless gum (28.4 mg, 0.166 mmol, 83%).

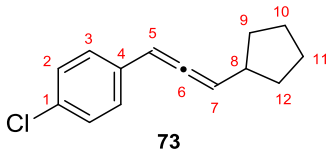
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 2 H, H3), 7.38 (d, *J* = 8.3 Hz, 2 H, H4), 6.33 (dt, *J* = 6.1, 2.9 Hz, 1 H, H6), 5.87 (q, *J* = 6.0 Hz, 1 H, H8), 4.33 – 4.27 (m, 2 H, H9), 1.65 (t, *J* = 5.9 Hz, 1 H, OH).
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8 (C7), 139.3 (C5), 132.6 (C3), 127.4 (C4), 119.1 (C1), 110.6 (C2), 96.9 (C8), 96.5 (C6), 60.1 (C9).
FTIR (ν_{max}, cm^{-1}): 3406 (br m, OH), 2875 (w), 2227 (s, C≡N), 1948 (m, C=C=C), 1605 (s), 1505 (m), 1415 (m), 1202 (w), 1175 (m), 1108 (m), 1016 (s), 876 (m), 844 (s).
HRMS (ESI): calculated for $C_{11}H_{10}NO$ $[M+H]^+$ 172.0757, found 172.0753.
***R*$_f$** = 0.22 (35% EtOAc/hexane).



72

(*E*)-6-Phenylhexa-2,3,5-trien-1-ol (72): Following the general procedure for allene formation with aldehyde-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and ((*E*)-3-phenylallylidene)hydrazine, purified by silica gel column chromatography (eluent: 25% EtOAc/hexane), provided the title compound as a yellow oil (16.4 mg, 0.095 mmol, 48%). Data are consistent with a reported example.[192]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.6 Hz, 2 H, H3), 7.31 (t, *J* = 7.6 Hz, 2 H, H2), 7.23 (t, *J* = 7.6 Hz, 1 H, H1), 6.61 (dd, *J* = 15.7, 10.3 Hz, 1 H, H6), 6.53 (d, *J* = 15.7 Hz, 1 H, H5), 6.17 (ddd, *J* = 10.3, 5.7, 2.8 Hz, 1 H, H7), 5.63 (q, *J* = 5.7 Hz, 1 H, H9), 4.21 (dt, *J* = 5.7, 2.8 Hz, 2 H, H10), 1.71 (br s, 1 H, OH).
^{13}C NMR (150 MHz, $CDCl_3$): δ 207.2 (C8), 137.1 (C4), 131.4 (C5), 128.7 (C2), 127.7 (C1), 126.4 (C3), 124.1 (C6), 97.4 (C7), 93.7 (C9), 60.6 (C10).
FTIR (ν_{max}, cm^{-1}): 3340 (m, OH), 3027 (w), 2929 (w), 1941 (m, C=C=C), 1597 (w), 1494 (w), 1450 (m), 1071 (m), 1009 (s), 964 (s), 877 (w).
HRMS (ESI): calculated for $C_{12}H_{13}O$ $[M+H]^+$ 173.0961, found 173.0958.
***R*$_f$** = 0.27 (25% EtOAc/hexane).



73

1-Chloro-4-(3-cyclopentylpropa-1,2-dien-1-yl)benzene (73): Following the general procedure for allene formation with aldehyde-derived hydrazones using cyclopentylacetylene (18.8 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (38.6 mg, 0.176 mmol, 88%).

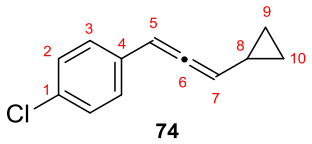
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2 H, H2), 7.20 (d, *J* = 8.6 Hz, 2 H, H3), 6.10 (dd, *J* = 6.4, 2.8 Hz, 1 H, H5), 5.63 (t, *J* = 6.4 Hz, 1 H, H7), 2.64 – 2.55 (m, 1 H, H8), 1.88 – 1.81 (m, 2 H, H9a and H12a), 1.72 – 1.54 (m, 4 H, H10 and H11), 1.49 – 1.41 (m, 2 H, H9b and H12b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.3 (C6), 133.9 (C1), 132.3 (C4), 128.8 (C2), 127.8 (C3), 100.6 (C7), 94.6 (C5), 39.3 (C8), 33.0 (C9/C12), 32.9 (C9/C12), 25.05 (C10/C11), 25.04 (C10/C11).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 2868 (w), 1950 (w, C=C=C), 1491 (s), 1453 (w), 1387 (w), 1092 (m), 1013 (w), 877 (w), 833 (m).

HRMS (ESI): calculated for $C_{14}H_{16}Cl$ $[M+H]^+$ 219.0935, found 219.0928.

***R*$_f$** = 0.68 (hexane).



74

1-Chloro-4-(3-cyclopropylpropa-1,2-dien-1-yl)benzene (74): Following the general procedure for allene formation with aldehyde-derived hydrazones using cyclopropylacetylene (**106**) (13.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (38.2 mg, 0.200 mmol, 99%).

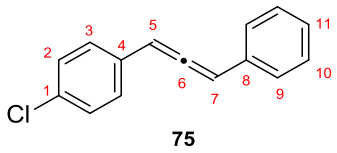
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 6.17 (d, *J* = 6.4 Hz, 1 H, H5), 5.45 (t, *J* = 6.4 Hz, 1 H, H7), 1.38 – 1.33 (m, 1 H, H8), 0.80 – 0.74 (m, 2 H, H9a and H10a), 0.50 – 0.40 (m, 2 H, H9b and H10b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.1 (C6), 133.6 (C4), 132.5 (C1), 128.8 (C2), 128.0 (C3), 100.1 (C7), 95.5 (C5), 9.5 (C8), 7.2 (C9/C10), 7.1 (C9/C10).

FTIR (ν_{max}, cm^{-1}): 3083 (w), 3005 (w), 1950 (w, C=C=C), 1490 (s), 1398 (w), 1252 (w), 1091 (s), 1048 (w), 1013 (m), 929 (w), 875 (m), 832 (s).

HRMS (ESI): calculated for $C_{12}H_{12}Cl$ $[M+H]^+$ 191.0622, found 191.0614.

R_f = 0.60 (hexane).



75

1-Chloro-4-(3-phenylpropa-1,2-dien-1-yl)benzene (75): Following the general procedure for allene formation with aldehyde-derived hydrazones using phenylacetylene (20.4 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a yellow oil (40.4 mg, 0.183 mmol, 92%). Data are consistent with a reported example.[193]

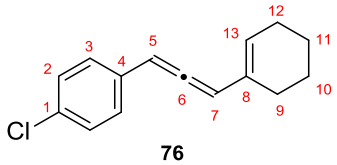
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.23 (m, 9 H, ArH), 6.61 (d, *J* = 6.6 Hz, 1 H, H5/H7), 6.56 (d, *J* = 6.6 Hz, 1 H, H5/H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 208.0 (C6), 133.4 (C1/C4/C8), 133.1 (C1/C4/C8), 132.3 (C1/C4/C8), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.7 (C11), 127.2 (CH), 99.0 (C5/C7), 97.7 (C5/C7).

FTIR (ν_{max}, cm^{-1}): 3030 (w), 1937 (w, C=C=C), 1597 (w), 1489 (s), 1458 (w), 1421 (w), 1386 (w), 1254 (w), 1193 (w), 1091 (s), 1013 (s), 964 (w), 913 (m), 878 (s), 832 (s).

HRMS (ESI): calculated for $C_{15}H_{12}Cl$ $[M+H]^+$ 227.0622, found 227.0614.

R_f = 0.45 (hexane).



76

1-Chloro-4-(3-(cyclohex-1-en-1-yl)propa-1,2-dien-1-yl)benzene (76): Following the general procedure for allene formation with aldehyde-derived hydrazones using 1-ethynylcyclohexene (21.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified

by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (29.0 mg, 0.126 mmol, 63%).

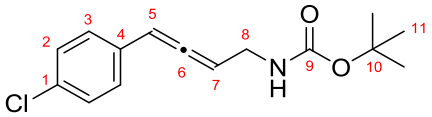
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2 H, H2), 7.22 (d, *J* = 8.6 Hz, 2 H, H3), 6.35 (br d, *J* = 6.4 Hz, 1 H, H7), 6.26 (d, *J* = 6.4 Hz, 1 H, H5), 5.78 (br s, 1 H, H13), 2.17 – 2.12 (m, 2 H, H12), 2.12 – 2.06 (m, 1 H, H9a), 2.02 – 1.94 (m, 1 H, H9b), 1.68 – 1.58 (m, 4 H, H10 and H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.7 (C6), 133.5 (C1), 132.6 (C4), 131.7 (C8), 128.9 (C2), 128.0 (C3), 127.7 (C13), 102.1 (C5), 96.8 (C7), 26.1 (C9/C12), 25.9 (C9/C12), 22.6 (C10/C11), 22.5 (C10/C11).

FTIR (ν_{max}, cm^{-1}): 2928 (m), 2858 (w), 2833 (w), 1932 (w, C=C=C), 1703 (w), 1592 (w), 1490 (s), 1448 (w), 1434 (w), 1386 (w), 1348 (w), 1250 (w), 1136 (w), 1092 (s), 1013 (s), 917 (w), 884 (m), 846 (s), 831 (s).

HRMS (ESI): calculated for $C_{15}H_{16}Cl$ $[M+H]^+$ 231.0935, found 231.0928.

***R*$_f$** = 0.53 (hexane).



77

***tert*-Butyl (4-(4-chlorophenyl)buta-2,3-dien-1-yl)carbamate (77):** Following the general procedure for allene formation with aldehyde-derived hydrazones using *N*-Boc-propargylamine (31.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) provided the title compound as a colourless oil (51.8 mg, 0.185 mmol, 93%).

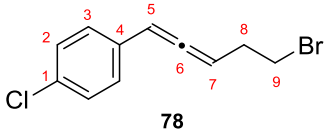
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2 H, H2), 7.20 (d, *J* = 8.5 Hz, 2 H, H3), 6.23 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.64 (q, *J* = 6.4 Hz, 1 H, H7), 4.74 (br s, 1 H, NH), 3.92 – 3.72 (m, 2 H, H8), 1.39 (s, 9 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 155.8 (C9), 132.9 (C1), 132.6 (C4), 128.9 (C2), 128.2 (C3), 96.6 (C5), 94.1 (C7), 79.7 (C10), 39.1 (C8), 28.5 (C11).

FTIR (ν_{max}, cm^{-1}): 3344 (w, NH), 2978 (w), 2932 (w), 1953 (w, C=C=C), 1690 (s, C=O), 1490 (s), 1455 (w), 1430 (w), 1391 (m), 1366 (m), 1273 (m), 1248 (s), 1162 (s), 1091 (m), 1051 (w), 1013 (m), 952 (w), 912 (w), 860 (w), 831 (m).

HRMS (ESI): calculated for $C_{15}H_{18}NO_2ClNa$ $[M+Na]^+$ 302.0918, found 302.0907.

R_f = 0.33 (15% EtOAc/hexane).



78

1-(5-Bromopenta-1,2-dien-1-yl)-4-chlorobenzene (78): Following the general procedure for allene formation with aldehyde-derived hydrazones using 4-bromo-1-butyne (26.6 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (42.2 mg, 0.164 mmol, 82%).

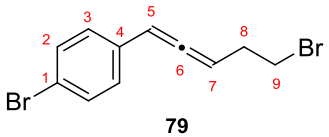
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H2), 7.24 (d, *J* = 8.6 Hz, 2 H, H3), 6.18 (dt, *J* = 6.6, 2.8 Hz, 1 H, H5), 5.62 (q, *J* = 6.6 Hz, 1 H, H7), 3.48 (td, *J* = 6.6, 1.2 Hz, 2 H, H9), 2.75 – 2.64 (m, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.0 (C6), 132.81 (C1/C4), 132.76 (C1/C4), 128.9 (C2), 128.2 (C3), 95.1 (C5), 93.0 (C7), 32.2 (C8), 31.8 (C9).

FTIR (ν_{max}, cm^{-1}): 2967 (w), 1950 (w, C=C=C), 1727 (m), 1589 (m), 1491 (s), 1402 (m), 1267 (m), 1208 (m), 1090 (s), 1014 (m), 873 (m), 832 (s).

HRMS (ESI): calculated for $C_{11}H_{11}BrCl$ $[M+H]^+$ 256.9727, found 256.9720.

R_f = 0.35 (hexane).



79

1-Bromo-4-(5-bromopenta-1,2-dien-1-yl)benzene (79): Following the general procedure for allene formation with aldehyde-derived hydrazones using 4-bromo-1-butyne (26.6 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (56.2 mg, 0.186 mmol, 93%).

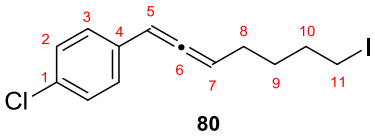
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2 H, H2), 7.18 (d, *J* = 8.5 Hz, 2 H, H3), 6.16 (dt, *J* = 6.6, 2.8 Hz, 1 H, H5), 5.61 (q, *J* = 6.6 Hz, 1 H, H7), 3.48 (td, *J* = 6.6, 1.1 Hz, 2 H, H9), 2.75 – 2.64 (m, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.9 (C6), 133.2 (C1), 131.8 (C2), 128.5 (C3), 120.8 (C4), 95.2 (C5), 93.1 (C7), 32.1 (C8), 31.8 (C9).

FTIR (ν_{max}, cm^{-1}): 2963 (w), 1949 (w, C=C=C), 1700 (w), 1588 (w), 1487 (s), 1429 (w), 1386 (w), 1265 (m), 1207 (m), 1102 (w), 1069 (s), 1009 (s), 964 (w), 928 (w), 871 (s), 828 (s).

HRMS (ESI): calculated for $C_{11}H_{11}Br_2$ $[M+H]^+$ 300.9222, found 300.9209.

***R*$_f$** = 0.27 (hexane).



80

1-Chloro-4-(7-iodohepta-1,2-dien-1-yl)benzene (80): Following the general procedure for allene formation with aldehyde-derived hydrazones using 6-iodo-1-hexyne (41.6 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (50.1 mg, 0.151 mmol, 75%).

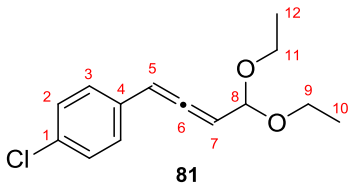
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2 H, H2), 7.20 (d, *J* = 8.5 Hz, 2 H, H3), 6.11 (dt, *J* = 6.6, 3.0 Hz, 1 H, H5), 5.57 (q, *J* = 6.6 Hz, 1 H, H7), 3.19 (t, *J* = 7.0 Hz, 2 H, H11), 2.20 – 2.12 (m, 2 H, H8), 1.94 – 1.86 (m, 2 H, H10), 1.65 – 1.54 (m, 2 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.4 (C6), 133.5 (C1), 132.4 (C4), 128.9 (C2), 127.9 (C3), 94.9 (C7), 94.3 (C5), 33.0 (C10), 29.9 (C9), 27.7 (C8), 6.6 (C11).

FTIR (ν_{max}, cm^{-1}): 2934 (w), 1949 (w, C=C=C), 1723 (m), 1703 (m), 1588 (m), 1490 (s), 1455 (m), 1427 (m), 1402 (m), 1265 (m), 1207 (m), 1169 (m), 1090 (s), 1013 (s), 878 (m), 820 (s).

HRMS (ESI): calculated for $C_{13}H_{15}ClI$ $[M+H]^+$ 332.9901, found 332.9894.

***R*$_f$** = 0.33 (hexane).

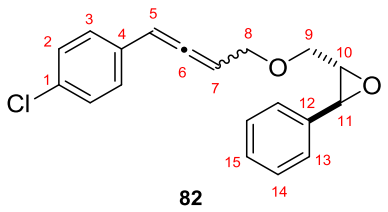


81

1-Chloro-4-(4,4-diethoxybuta-1,2-dien-1-yl)benzene (81): Following the general procedure for allene formation with aldehyde-derived hydrazones using 3,3-diethoxy-1-propyne

(25.6 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 4% EtOAc/hexane) provided the title compound as a colourless gum (47.8 mg, 0.199 mmol, 99%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H2), 7.22 (d, *J* = 8.6 Hz, 2 H, H3), 6.28 (dd, *J* = 6.1, 1.5 Hz, 1 H, H5), 5.66 (t, *J* = 6.1 Hz, 1 H, H7), 5.06 (dd, *J* = 6.1, 1.5 Hz, 1 H, H8), 3.71 (dq overlaps with 3.68 peak, *J* = 9.5, 7.1 Hz, 1 H, H9a/H11a), 3.68 (dq overlaps with 3.71 peak, *J* = 9.5, 7.1 Hz, 1 H, H9a/H11a), 3.58 (two superimposed tq, *J* = 9.5, 7.1 Hz, 2 H, H9b and H11b), 1.24 (t, *J* = 7.1 Hz, 3 H, H10/H12), 1.23 (t, *J* = 7.1 Hz, 3 H, H10/H12).
^{13}C NMR (150 MHz, $CDCl_3$): δ 205.8 (C6), 133.0 (C4), 132.3 (C1), 128.9 (C2), 128.2 (C3), 100.2 (C8), 96.0 (C5), 95.4 (C7), 61.7 (C9/C11), 61.5 (C9/C11), 15.31 (C10/C12), 15.28 (C10/C12).
FTIR (ν_{max}, cm^{-1}): 2976 (w), 2881 (w), 1956 (w, C=C=C), 1491 (m), 1432 (w), 1388 (w), 1330 (w), 1090 (s), 1053 (s), 1013 (m), 872 (w), 833 (m).
HRMS (ESI): calculated for $C_{14}H_{17}OClNa$ $[M+Na]^+$ 275.0809, found 275.0800.
R_f = 0.31 (4% EtOAc/hexane).



82

(2*RS*,3*RS*)-2-(((4-(4-Chlorophenyl)buta-2,3-dien-1-yl)oxy)methyl)-3-phenyloxirane (82): Following the general procedure for allene formation with aldehyde-derived hydrazones using (2*RS*,3*RS*)-2-phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane (37.6 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a colourless oil (55.4 mg, 0.177 mmol, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2 H, H14), 7.33 – 7.29 (m, 1 H, H15), 7.29 – 7.25 (m, 4 H, H2 and H13), 7.23 (two superimposed d, *J* = 8.3 Hz, 2 H, H3), 6.26 – 6.22 (m, 1 H, H5), 5.72 (two superimposed q, *J* = 6.5 Hz, 1 H, H7), 4.26 – 4.22 (m, 2 H, H8), 3.89

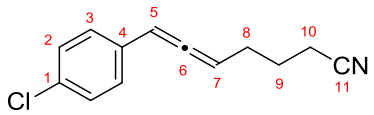
(two superimposed ddd, *J* = 11.5, 8.9, 3.0 Hz, 1 H, H9a), 3.80 (two superimposed dd, *J* = 7.5, 3.0 Hz, 1 H, H11), 3.68 – 3.66 (m, 1 H, H9b), 3.25 – 3.22 (m, 1 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.16 and 206.13 (C6), 136.87 and 136.86 (C12), 132.89 and 132.88 (C4), 132.45 and 132.44 (C1), 128.94 and 128.93 (C2), 128.6 (C14), 128.4 (C15), 128.16 and 128.15 (C3), 125.81 and 125.80 (C13), 95.0 (C5), 92.9 (C7), 69.92 and 69.91 (C9), 69.03 and 69.01 (C8), 61.1 (C10), 56.04 and 56.01 (C11).

FTIR (ν_{max}, cm^{-1}): 2990 (w), 2857 (w), 1951 (w, C=C=C), 1490 (m), 1462 (w), 1431 (w), 1391 (w), 1352 (w), 1308 (w), 1242 (w), 1201 (w), 1090 (s), 1013 (m), 969 (w), 873 (s), 832 (s).

HRMS (ESI): calculated for $C_{19}H_{17}O_2ClNa$ $[M+Na]^+$ 335.0809, found 335.0804.

***R*$_f$** = 0.30 (10% EtOAc/hexane).



83

7-(4-Chlorophenyl)hepta-5,6-dienenitrile (83): Following the general procedure for allene formation with aldehyde-derived hydrazones using 5-hexynenitrile (18.6 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) provided the title compound as a colourless oil (40.7 mg, 0.187 mmol, 93%).

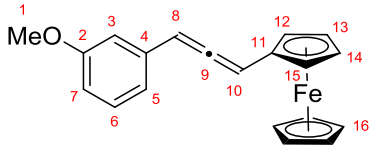
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H2), 7.19 (d, *J* = 8.6 Hz, 2 H, H3), 6.16 (dt, *J* = 6.4, 3.1 Hz, 1 H, H5), 5.59 (q, *J* = 6.4 Hz, 1 H, H7), 2.40 (t, *J* = 7.1 Hz, 2 H, H10), 2.33 – 2.26 (m, 2 H, H8), 1.90 – 1.79 (m, 2 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.5 (C6), 133.0 (C1), 132.7 (C4), 129.0 (C2), 127.9 (C3), 119.4 (C11), 95.1 (C5), 93.6 (C7), 27.4 (C8), 24.6 (C9), 16.7 (C10).

FTIR (ν_{max}, cm^{-1}): 2937 (w), 2247 (w, C≡N), 1950 (w, C=C=C), 1732 (w), 1591 (w), 1499 (s), 1424 (w), 1390 (w), 1260 (w), 1174 (w), 1089 (s), 1013 (m), 880 (m), 832 (s).

HRMS (ESI): calculated for $C_{13}H_{13}NCl$ $[M+H]^+$ 218.0731, found 218.0722.

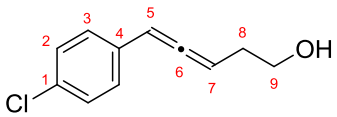
***R*$_f$** = 0.25 (15% EtOAc/hexane).



84

3-(4-Chloro)phenylpropa-1,2-dienylferrocene (84): Following the general procedure for allene formation with aldehyde-derived hydrazones using ethynylferrocene (42.0 mg, 0.2 mmol) and (3-methoxybenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 4% EtOAc/hexane), provided the title compound as a red oil (61.0 mg, 0.185 mmol, 92%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (t, *J* = 8.1 Hz, 1 H, H6), 6.98 (d, *J* = 8.1 Hz, 1 H, H5), 6.94 (s, 1 H, H3), 6.81 (d, *J* = 8.1 Hz, 1 H, H7), 6.34 (d, *J* = 6.4 Hz, 1 H, H10), 6.31 (d, *J* = 6.4 Hz, 1 H, H8), 4.36 (s, 1 H, H12/H15), 4.32 (s, 1 H, H12/H15), 4.23 (s, 2 H, H13 and H14), 4.21 (s, 5 H, H16), 3.83 (s, 3 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 206.2 (C9), 160.0 (C2), 135.8 (C4), 129.7 (C6), 119.6 (C5), 112.9 (C7), 112.1 (C3), 97.2 (C8), 95.2 (C10), 79.7 (C11), 69.4 (C16), 68.8 (C13/C14), 68.7 (C13/C14), 67.7 (C12/C15), 67.1 (C12/C15), 55.3 (C1).
FTIR (ν_{max}, cm^{-1}): 3086 (w), 2939 (w), 2834 (w), 1936 (w, C=C=C), 1595 (m), 1581 (m), 1488 (m), 1464 (m), 1452 (m), 1435 (m), 1410 (w), 1316 (w), 1291 (m), 1264 (s), 1224 (m), 1152 (m), 1105 (m), 1044 (s), 1000 (m), 924 (w), 873 (m), 817 (s).
HRMS (ESI): calculated for $C_{20}H_{18}OFe$ $[M]^+$ 330.0702, found 330.0687.
R_f = 0.41 (4% EtOAc/hexane).



85

5-(4-Chlorophenyl)penta-3,4-dien-1-ol (85): Following the general procedure for allene formation with aldehyde-derived hydrazones using 3-butyn-1-ol (14.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a colourless oil (35.2 mg, 0.181 mmol, 90%).

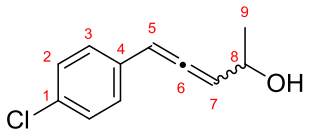
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2 H, H2), 7.21 (d, *J* = 8.6 Hz, 2 H, H3), 6.14 (dt, *J* = 6.6, 2.9 Hz, 1 H, H5), 5.61 (q, *J* = 6.6 Hz, 1 H, H7), 3.77 (t, *J* = 6.2 Hz, 2 H, H9), 2.43 – 2.35 (m, 2 H, H8), 1.69 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.9 (C6), 133.1 (C1), 132.6 (C4), 128.9 (C2), 127.9 (C3), 94.3 (C5), 92.0 (C7), 62.0 (C9), 32.1 (C8).

FTIR (ν_{max}, cm^{-1}): 3319 (br w, OH), 2284 (w), 1952 (w, C=C=C), 1491 (s), 1390 (w), 1090 (m), 1048 (m), 1013 (m), 877 (m), 834 (m).

HRMS (ESI): calculated for $C_{11}H_{12}OCl$ $[M+H]^+$ 195.0571, found 195.0564.

***R*$_f$** = 0.22 (25% EtOAc/hexane).



86

5-(4-Chlorophenyl)penta-3,4-dien-2-ol (86): Following the general procedure for allene formation with aldehyde-derived hydrazones using 3-butyn-2-ol (14.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a colourless oil (30.2 mg, 0.165 mmol, 83%).

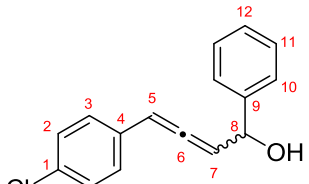
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (two superimposed d, *J* = 8.5 Hz, 2 H, H2), 7.21 (two d, *J* = 8.5 Hz, 2 H, H3), 6.28 – 6.25 (m, 1 H, H5), 5.74 (two t, *J* = 6.0 Hz, 1 H, H7), 4.52 – 4.44 (m, 1 H, H8), 1.83 (two superimposed br s, 1 H, OH), 1.38 (two d, *J* = 6.4 Hz, 3 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.40 and 203.37 (C6), 132.9 (C1), 132.63 and 132.56 (C4), 129.0 (C2), 128.04 and 128.03 (C3), 101.38 and 101.37 (C7), 96.8 and 96.6 (C5), 66.26 and 66.00 (C8), 23.79 and 23.71 (C9).

FTIR (ν_{max}, cm^{-1}): 3358 (br w, OH), 2978 (w), 1951 (w, C=C=C), 1701 (m), 1590 (m), 1490 (m), 1402 (m), 1376 (m), 1265 (m), 1207 (m), 1172 (m), 1090 (s), 1013 (s), 924 (m), 878 (m), 821 (s).

HRMS (ESI+): calculated for $C_{11}H_{12}OCl$ $[M+H]^+$ 195.0571, found 195.0565.

***R*$_f$** = 0.25 (20% EtOAc/hexane).



87

4-(4-Chlorophenyl)-1-phenylbuta-2,3-dien-1-ol (87): Following the general procedure for allene formation with aldehyde-derived hydrazones using 3-butyn-2-ol (14.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 15% EtOAc/hexane), provided the title compound as separable diastereomers (1:1) as off-white amorphous solids (A: 23.7 mg, 0.092 mmol; B: 26.3 mg, 0.102 mmol; combined yield 97%), m.p. 85-88 °C for diastereomer A and m.p. 92-95 °C for diastereomer B.

Diastereomer A:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.3 Hz, 2 H, H10), 7.39 (t, *J* = 7.3 Hz, 2 H, H11), 7.32 (t, *J* = 7.3 Hz, 1 H, H12), 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.24 (d, *J* = 8.5 Hz, 2 H, H3), 6.33 (dd, *J* = 6.2, 2.5 Hz, 1 H, H5), 5.90 (t, *J* = 6.2 Hz, 1 H, H7), 5.39 – 5.35 (m, 1 H, H8), 2.19 (br d, *J* = 3.7 Hz, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.8 (C6), 142.8 (C9), 133.1 (C4), 132.4 (C1), 129.0 (C2), 128.8 (C11), 128.21 (C3), 128.17 (C12), 126.2 (C10), 100.6 (C7), 97.4 (C5), 72.3 (C8).

FTIR (ν_{max}, cm^{-1}): 3295 (br m, OH), 3062 (w), 1950 (w, C=C=C), 1499 (s), 1450 (m), 1430 (w), 1192 (w), 1090 (m), 1013 (s), 879 (m), 841 (m).

HRMS (ESI): calculated for $C_{16}H_{14}OCl$ $[M+H]^+$ 257.0728, found 257.0717.

R_f = 0.25 (15% EtOAc/hexane).

Diastereomer B:

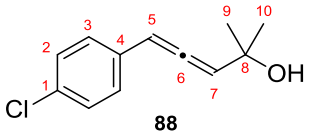
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.3 Hz, 2 H, H10), 7.38 (t, *J* = 7.3 Hz, 2 H, H11), 7.32 (t, *J* = 7.3 Hz, 1 H, H12), 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.18 (d, *J* = 8.5 Hz, 2 H, H3), 6.33 (dd, *J* = 6.3, 2.2 Hz, 1 H, H4), 5.89 (t, *J* = 6.3 Hz, 1 H, H7), 5.42 – 5.38 (m, 1 H, H8), 2.20 (br d, *J* = 6.6 Hz, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.1 (C6), 142.9 (C9), 133.1 (C4), 132.4 (C1), 129.0 (C2), 128.8 (C11), 128.17 (C3), 128.16 (C12), 126.1 (C10), 100.5 (C7), 97.1 (C5), 72.5 (C8).

FTIR (ν_{max}, cm^{-1}): 3390 (br w, OH), 3066 (w), 3033 (w), 1949 (w, C=C=C), 1490 (s), 1455 (m), 1426 (w), 1386 (w), 1254 (m), 1197 (w), 1109 (w), 1090 (s), 1045 (m), 1028 (w), 1012 (m), 922 (w), 886 (m), 840 (s), 828 (m), 814 (w).

HRMS (ESI): calculated for $C_{16}H_{14}OCl$ $[M+H]^+$ 257.0728, found 257.0717.

$\boldsymbol{R_f}$ = 0.21 (15% EtOAc/hexane).



88

5-(4-Chlorophenyl)-2-methylpenta-3,4-dien-2-ol (88): Following the general procedure for allene formation with aldehyde-derived hydrazones using 2-methyl-3-butyn-2-ol (16.8 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a colourless oil (34.0 mg, 0.163 mmol, 82%).

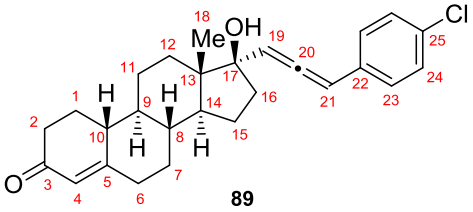
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 6.28 (d, *J* = 6.4 Hz, 1 H, H5), 5.80 (d, *J* = 6.4 Hz, 1 H, H7), 1.83 (br s, 1 H, OH), 1.429 (s, 3 H, H9/H10), 1.426 (s, 3 H, H9/H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 202.2 (C6), 132.9 (C4), 132.7 (C1), 129.0 (C2), 127.9 (C3), 105.6 (C7), 97.1 (C5), 70.4 (C8), 30.3 (C9/C10), 30.2 (C9/C10).

FTIR (ν_{max}, cm^{-1}): 3368 (br w, OH), 2976 (m), 2931 (w), 1951 (w, C=C=C), 1700 (m), 1592 (w), 1491 (s), 1426 (w), 1375 (m), 1149 (s), 1092 (s), 1014 (s), 967 (m), 878 (m), 834 (s).

HRMS (ESI): calculated for $C_{12}H_{14}OCl$ $[M+H]^+$ 209.0728, found 209.0720.

$\boldsymbol{R_f}$ = 0.26 (20% EtOAc/hexane).



89

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-(3-(4-Chlorophenyl)propa-1,2-dien-1-yl)-17-hydroxy-13-methyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (89): Following the general procedure for allene formation with aldehyde-derived hydrazones using norethindrone (59.7 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (diastereomer A – eluent: 40% EtOAc/hexane, then 80% Et_2O/hexane; diastereomer B –

eluent: 40% EtOAc/hexane), provided the title compound as separable diastereomers (1.5:1) as off-white foams (A: 33.6 mg, 0.079 mmol; B: 20.0 mg, 0.047 mmol; combined yield 63%).

Diastereomer A:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H24), 7.23 (d, *J* = 8.6 Hz, 2 H, H23), 6.30 (d, *J* = 6.2 Hz, 1 H, H21), 5.84 (s, 1 H, H4), 5.80 (d, *J* = 6.2 Hz, 1 H, H19), 2.51 – 2.40 (m, 2 H, steroidal H/OH), 2.31 – 2.24 (m, 3 H, steroidal H/OH), 2.14 – 2.09 (m, 1 H, steroidal H/OH), 2.05 – 1.99 (m, 1 H, steroidal H/OH), 1.94 – 1.83 (m, 3 H, steroidal H/OH), 1.67 – 1.45 (m, 4 H, steroidal H/OH), 1.42 – 1.25 (m, 5 H, steroidal H/OH), 1.11 – 1.03 (m, 1 H, steroidal H/OH), 0.99 (s, 3 H, H18), 0.91 – 0.84 (m, 1 H, steroidal H/OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 202.6 (C20), 200.0 (C3), 166.7 (C5), 133.0 (C22), 132.8 (C25), 129.0 (C24), 128.0 (C23), 124.7 (C4), 102.8 (C21), 97.2 (C19), 83.6 (C17), 49.5 (CH), 48.9 (C14), 47.1 (C13), 42.7 (C10), 41.2 (CH), 36.72 (CH_2), 36.65 (CH_2), 35.6 (CH_2), 32.4 C12), 31.0 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 23.5 (CH_2), 14.2 (C18).

FTIR (ν_{max}, cm^{-1}): 3409 (br w, OH), 2932 (m), 2867 (m), 1945 (w, C=C=C), 1660 (s, C=O), 1491 (m), 1452 (w), 1428 (w), 1362 (w), 1332 (w), 1261 (w), 1208 (w), 1130 (w), 1091 (w), 1063 (w), 1013 (m), 968 (w), 910 (w), 883 (w), 837 (w).

HRMS (ESI): calculated for $C_{27}H_{32}OCl$ $[M+H]^+$ 423.2085, found 423.2069.

R_f = 0.29 (40% EtOAc/hexane); 0.36 (80% Et_2O/hexane).

Diastereomer B:

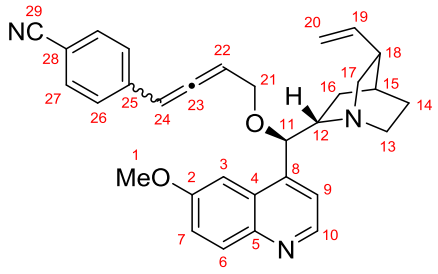
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2 H, H24), 7.19 (d, *J* = 8.5 Hz, 2 H, H23), 6.30 (d, *J* = 6.3 Hz, 1 H, H21), 5.85 (s, 1 H, H4), 5.81 (d, *J* = 6.3 Hz, 1 H, H19), 2.48 – 2.40 (m, 2 H, steroidal H), 2.33 – 2.23 (m, 3 H, steroidal H), 2.16 – 2.09 (m, 2 H, steroidal H), 1.95 – 1.87 (m, 2 H, steroidal H), 1.84 (br s, 1 H, OH), 1.79 – 1.74 (m, 1 H, steroidal H), 1.69 – 1.64 (m, 1 H, steroidal H), 1.61 – 1.55 (m, 1 H, steroidal H), 1.53 – 1.47 (m, 2 H, steroidal H), 1.42 – 1.25 (m, 4 H, steroidal H), 0.99 (s, 3 H, H18), 0.89 – 0.80 (m, 2 H, steroidal H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.1 (C20), 200.0 (C3), 166.5 (C5), 133.0 (C22), 132.8 (C25), 128.9 (C24), 128.0 (C23), 124.8 (C4), 102.2 (C21), 97.0 (C19), 83.4 (C17), 49.8 (CH), 48.7 (C14), 46.8 (C13), 42.7 (C10), 41.1 (CH), 36.7 (CH_2), 36.4 (CH_2), 35.5 (CH_2), 32.2 (C12), 30.9 (CH_2), 26.8 (CH_2), 26.2 (CH_2), 23.2 (CH_2), 14.1 (C18).

FTIR (ν_{max}, cm^{-1}): 3421 (br w, OH), 2932 (m), 2866 (m), 1946 (w, C=C=C), 1660 (s, C=O), 1491 (m), 1451 (w), 1427 (w), 1362 (w), 1332 (w), 1261 (w), 1208 (w), 1131 (w), 1091 (m), 1060 (w), 1013 (m), 967 (w), 883 (w), 836 (w).

HRMS (ESI): calculated for $C_{27}H_{32}OCl$ $[M+H]^+$ 423.2085, found 423.2069.

R_f = 0.23 (40% EtOAc/hexane).



90

4-(4-((1*R*)-(6-Methoxyquinolin-4-yl)((2*S*)-5-vinylquinuclidin-2-yl)methoxy)buta-1,2-dien-1-yl)benzonitrile (90): Following the general procedure for allene formation with aldehyde-derived hydrazones using norethindrone (59.7 mg, 0.2 mmol) and 4-(hydrazonomethyl)benzonitrile, purified by silica gel column chromatography (eluent: 30% EtOAc/60% hexane/10% Et_3N), provided the title compound as an inseparable mixture of diastereomers (1:1) as a brown film (78.3 mg, 0.164 mmol, 82%).

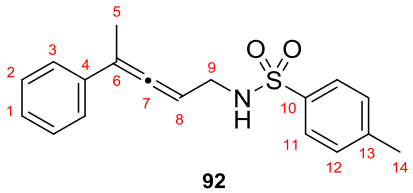
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75 – 8.68 (m, 1 H, H10), 8.01 (m, 1 H, H6), 7.57 – 7.20 (m, 7 H, ArH), 6.21 (m, 1 H, H24), 5.82 – 5.72 (m, 1 H, H22), 5.66 (m, 1 H, H19), 5.23 (br s, 1 H, H11), 4.95 – 4.80 (m, 2 H, H20), 4.16 – 3.95 (m, 2 H, H21), 3.93 – 3.84 (m, 3 H, H1), 3.37 – 3.21 (m, 1 H, H13a), 3.12 – 2.98 (m, 2 H, H12 and H17a), 2.71 – 2.53 (m, 2 H, H13b and H17b), 2.28 – 2.16 (m, 1 H, H18), 1.80 – 1.32 (m, 5 H, H14, H15 and H16).

^{13}C NMR (150 MHz, $CDCl_3$): δ 207.2 and 206.8 (C23), 157.9 (C2), 147.6 (C10), 144.6 (C8), 144.3 (C5), 141.9 (C19), 139.08 and 139.05 (C25), 132.44 and 132.38 (C27), 131.9 (C6), 127.32 and 127.22 (C26), 127.19 (C4), 121.7 and 121.6 (C7), 119.5 – 118.5 (br, C9), 119.0 (C29), 114.4 (C20), 110.34 and 110.29 (C28), 101.2 (br, C3), 95.5 and 95.2 (C24), 93.8 and 93.5 (C22), 77.5 – 77.0 (br, obscured by $CDCl_3$ peak, C11), 66.4 and 66.3 (C21), 60.0 (C12), 57.3 (C17), 55.79 and 55.71 (C1), 43.4 (C13), 40.01 and 39.95 (C18), 27.87 and 27.83 (C15), 27.78 and 27.6 (C14), 24.0 – 20.0 (br, C16).

FTIR (ν_{max}, cm^{-1}): 2935 (m), 2865 (w), 2225 (m, C≡N), 1950 (w, C=C=C), 1620 (s), 1605 (m), 1507 (s), 1472 (m), 1454 (m), 1432 (m), 1355 (w), 1301 (w), 1259 (m), 1240 (s), 1227 (s), 1174 (w), 1133 (m), 1076 (s), 1030 (s), 992 (w), 910 (s), 875 (m), 843 (s), 831 (s).

HRMS (ESI): calculated for $C_{31}H_{32}N_3O_2$ $[M+H]^+$ 478.2489, found 478.2481.

R_f = 0.28 (30% EtOAc/60% hexane/10% Et_3N).



92

4-Methyl-*N*-(4-phenylpenta-2,3-dien-1-yl)benzenesulfonamide (92): Following the general procedure for allene formation with ketone-derived hydrazones using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol) and (1-phenylethylidene)hydrazine (**91**), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a colourless oil (41.7 mg, 0.133 mmol, 67%).

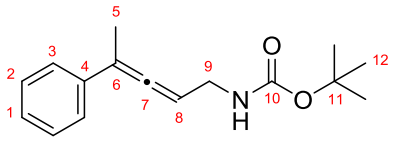
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2 H, H11), 7.31 (m, 4 H, H2 and H3), 7.27 (d, *J* = 8.2 Hz, 2 H, H12), 7.25 – 7.21 (m, 1 H, H1), 5.42 (tq, *J* = 5.9, 2.9 Hz, 1 H, H8), 4.66 (t, *J* = 5.9 Hz, 1 H, NH), 3.67 (t, *J* = 5.9 Hz, 2 H, H9), 2.41 (s, 3 H, H14), 2.05 (d, *J* = 2.9 Hz, 3 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.6 (C7), 143.6 (C4), 137.0 (C10), 136.2 (C13), 129.9 (C12), 128.5 (C2/C3), 127.31 (C1), 127.26 (C11), 125.9 (C2/C3), 104.4 (C6), 90.0 (C8), 42.1 (C9), 21.7 (C14), 17.1 (C5).

FTIR (ν_{max}, cm^{-1}): 3292 (br w, NH), 2924 (w), 1950 (w, C=C=C), 1723 (w), 1681 (w), 1598 (w), 1494 (w), 1447 (w), 1327 (m), 1267 (w), 1155 (s), 1091 (m), 909 (m), 813 (m).

HRMS (ESI): calculated for $C_{18}H_{19}NO_2SNa$ $[M+Na]^+$ 336.1029, found 336.1022.

***R*$_f$** = 0.26 (20% EtOAc/hexane).



95

***tert*-Butyl (4-phenylpenta-2,3-dien-1-yl)carbamate (95):** Following the general procedure for allene formation with ketone-derived hydrazones using *N*-Boc-propargylamine (**239**) (31.0 mg, 0.2 mmol) and (1-phenylethylidene)hydrazine (**91**), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (38.2 mg, 0.147 mmol, 74%).

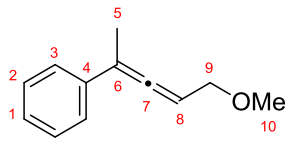
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.6 Hz, 2 H, H3), 7.32 (t, *J* = 7.6 Hz, 2 H, H2), 7.22 (t, *J* = 7.6 Hz, 1 H, H1), 5.56 – 5.48 (m, 1 H, H8), 4.69 (s, 1 H, NH), 3.82 (br s, 2 H, H9), 2.12 (d, *J* = 2.9 Hz, 3 H, H5), 1.42 (s, 9 H, H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.5 (C7), 155.8 (C10), 136.8 (C4), 128.5 (C2), 127.0 (C1), 125.9 (C3), 103.6 (C6), 91.5 (C8), 79.5 (C11), 39.5 (C9), 28.5 (C12), 17.2 (C5).

FTIR (ν_{max}, cm^{-1}): 3354 (br w, NH), 2978 (w), 2930 (w), 1952 (w, C=C=C), 1690 (s, C=O), 1598 (w), 1495 (m), 1446 (w), 1391 (w), 1366 (m), 1247 (s), 1164 (s), 1067 (w), 1050 (w), 1026 (w), 941 (w), 909 (w), 860 (w).

HRMS (ESI): calculated for $C_{16}H_{21}NO_2Na$ $[M+Na]^+$ 282.1465, found 282.1454.

***R*$_f$** = 0.32 (10% EtOAc/hexane).



96

(5-Methoxypenta-2,3-dien-2-yl)benzene (96): Following the general procedure for allene formation with ketone-derived hydrazones using methyl propargyl ether (14.0 mg, 0.2 mmol) and (1-phenylethylidene)hydrazine (**91**), purified by silica gel column chromatography (eluent: 5% EtOAc/hexane) provided the title compound as a colourless oil (22.8 mg, 0.131 mmol, 65%).

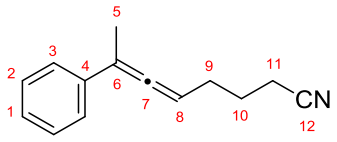
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.3 Hz, 2 H, H3), 7.33 (t, *J* = 7.3 Hz, 2 H, H2), 7.22 (t, *J* = 7.3 Hz, 1 H, H1), 5.55 (tq, *J* = 6.8, 2.9 Hz, 1 H, H8), 4.05 (d, *J* = 6.8 Hz, 2 H, H9), 3.39 (s, 3 H, H10), 2.14 (d, *J* = 2.9 Hz, 3 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.2 (C7), 136.8 (C4), 128.5 (C2), 126.9 (C1), 125.9 (C3), 101.5 (C6), 90.5 (C8), 70.8 (C9), 57.9 (C10), 17.2 (C5).

FTIR (ν_{max}, cm^{-1}): 2982 (w), 2927 (w), 2817 (w), 1952 (w, C=C=C), 1741 (w), 1598 (w), 1494 (m), 1445 (m), 1351 (w), 1262 (w), 1185 (w), 1099 (s), 1067 (m), 1027 (w), 957 (w), 913 (m).

HRMS (ESI): calculated for $C_{12}H_{15}O$ $[M+H]^+$ 175.1117, found 175.1112.

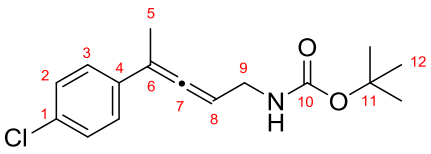
***R*$_f$** = 0.33 (5% EtOAc/hexane).



97

7-Phenylocta-5,6-dienenitrile (97): Following the general procedure for allene formation with ketone-derived hydrazones using 5-hexynenitrile (18.6 mg, 0.2 mmol) and (1-phenylethylidene)hydrazine (**91**), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (29.0 mg, 0.147 mmol, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.4 Hz, 2 H, H3), 7.33 (t, *J* = 7.4 Hz, 2 H, H2), 7.22 (t, *J* = 7.4 Hz, 1 H, H1), 5.46 (tq, *J* = 7.1, 2.9 Hz, 1 H, H8), 2.40 (t, *J* = 7.2 Hz, 2 H, H11), 2.27 (q, *J* = 7.1 Hz, 2 H, H9), 2.11 (d, *J* = 2.9 Hz, 3 H, H5), 1.90 – 1.78 (m, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 204.5 (C7), 137.1 (C4), 128.5 (C2), 126.9 (C1), 125.7 (C3), 119.7 (C12), 101.9 (C6), 91.1 (C8), 27.8 (C9), 24.7 (C10), 17.3 (C5), 16.6 (C11).
FTIR (ν_{max}, cm^{-1}): 2940 (w), 2247 (w, C≡N), 1951 (w, C=C=C), 1727 (w), 1685 (w), 1598 (w), 1493 (s), 1445 (s), 1371 (w), 1288 (w), 1264 (w), 1183 (w), 1067 (m), 1026 (m), 912 (w), 844 (w).
HRMS (ESI): calculated for $C_{14}H_{16}N$ $[M+H]^+$ 198.1277, found 198.1270.
***R*$_f$** = 0.33 (10% EtOAc/hexane).



98

***tert*-Butyl (4-(4-chlorophenyl)penta-2,3-dien-1-yl)carbamate (98):** Following the general procedure for allene formation with ketone-derived hydrazones using *N*-Boc-propargylamine (**239**) (31.0 mg, 0.2 mmol) and (1-(4-chlorophenyl)ethylidene)hydrazine (**237**), purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) provided the title compound as a colourless oil (52.4 mg, 0.178 mmol, 89%).

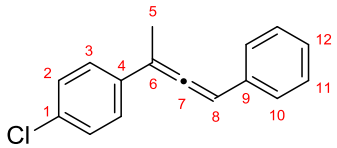
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.6 Hz, 2 H, H2), 7.26 (d, *J* = 8.6 Hz, 2 H, H3), 5.53 – 5.47 (m, 1 H, H8), 4.69 (br s, 1 H, NH), 3.85 – 3.73 (m, 2 H, H9), 2.07 (d, *J* = 2.9 Hz, 3 H, H5), 1.40 (s, 9 H, H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.5 (C7), 155.8 (C10), 135.4 (C4), 132.7 (C1), 128.5 (C3), 127.2 (C2), 102.8 (C6), 92.0 (C8), 79.6 (C11), 39.4 (C9), 28.5 (C12), 17.2 (C5).

FTIR (ν_{max}, cm^{-1}): 3348 (br w, NH), 2978 (w), 2931 (w), 1954 (w, C=C=C), 1690 (s, C=O), 1490 (s), 1455 (w), 1392 (m), 1366 (m), 1249 (m), 1165 (s), 1095 (m), 1063 (w), 1012 (m), 941 (w), 860 (w), 831 (w).

HRMS (ESI): calculated for $C_{16}H_{20}NO_2ClNa$ $[M+Na]^+$ 316.1075, found 316.1067.

R_f = 0.41 (15% EtOAc/hexane).



99

1-Chloro-4-(4-phenylbuta-2,3-dien-2-yl)benzene (99): Following the general procedure for allene formation with ketone-derived hydrazones using phenylacetylene (20.4 mg, 0.2 mmol) and (1-(4-chlorophenyl)ethylidene)hydrazine (**237**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a yellow oil (52.4 mg, 0.178 mmol, 89%). Data are consistent with a reported example.[96]

Scale up to 5 mmol was possible using a slightly modified procedure as follows: A 250 mL round-bottomed flask was charged with phenylacetylene (0.51 g, 5.0 mmol, 1.0 equiv.), copper(I) iodide (95 mg, 0.5 mmol, 0.1 equiv.), 2,6-lutidine (0.12 mL, 1.0 mmol, 0.2 equiv.), 1,4-dioxane (50 mL), Et_3N (1.39 mL, 10.0 mmol, 2.0 equiv.) and pre-mixed for 10 min. A solution of (1-(4-chlorophenyl)ethylidene)hydrazine (**237**) (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through the column reactor (Omnifit® column, 0.79 cm i.d. × 15.0 cm length), packed with activated MnO_2 (12.0 g), at a flow rate of 4.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak was stable, 75 mL of the output (1.5 equiv. with respect to the hydrazone) was directly added into the reaction flask (over 17 min) containing the copper acetylide and the reaction mixture further stirred at r.t. for 10 min. The mixture was then filtered through a pad of Celite, eluting with EtOAc, and the filtrate evaporated under reduced pressure. The residue was immediately purified by silica gel column chromatography (eluent: hexane) to provide the title compound as a yellow oil (0.88 g, 3.66 mmol, 73%).

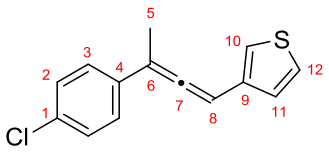
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.6 Hz, 2 H, H2), 7.34 – 7.31 (m, 4 H, H10 and H11), 7.29 (d, *J* = 8.6 Hz, 2 H, H3), 7.26 – 7.21 (m, 1 H, H12), 6.49 (q, *J* = 2.9 Hz, 1 H, H8), 2.21 (d, *J* = 2.9 Hz, 3 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.9 (C7), 135.0 (C4), 134.3 (C9), 132.9 (C1), 128.9 (C10/C11), 128.7 (C3), 127.3 (C12), 127.2 (C2), 127.1 (C10/C11), 103.9 (C6), 97.1 (C8), 16.90 (C5).

FTIR (ν_{max}, cm^{-1}): 3028 (w), 1934 (w, C=C=C), 1689 (w), 1597 (w), 1489 (s), 1449 (w), 1408 (w), 1257 (w), 1198 (w), 1093 (s), 1062 (w), 1012 (s), 913 (w), 833 (s), 818 (s).

HRMS (ESI): calculated for $C_{16}H_{14}Cl$ $[M+H]^+$ 241.0779, found 241.0770.

***R*$_f$** = 0.39 (hexane).



100

3-(3-(4-Chlorophenyl)buta-1,2-dien-1-yl)thiophene (100): Following the general procedure for allene formation with ketone-derived hydrazones using 3-ethynylthiophene (21.6 mg, 0.2 mmol) and (1-(4-chlorophenyl)ethylidene)hydrazine (**237**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a yellow oil (26.3 mg, 0.107 mmol, 53%).

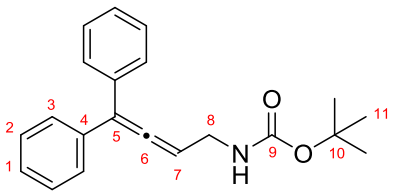
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.6 Hz, 2 H, H2), 7.28 (d, *J* = 8.6 Hz, 2 H, H3), 7.27 (dd, *J* = 5.0, 2.9 Hz, 1 H, H11), 7.14 (dd, *J* = 2.9, 1.2 Hz, 1 H, H10), 7.05 (dd, *J* = 5.0, 1.2 Hz, 1 H, H12), 6.55 (q, *J* = 2.9 Hz, 1 H, H8), 2.18 (d, *J* = 2.9 Hz, 3 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 207.0 (C7), 135.6 (C9), 135.2 (C4), 132.9 (C1), 128.7 (C3), 127.3 (C2), 126.5 (C12), 126.2 (C11), 121.3 (C10), 103.0 (C6), 91.6 (C8), 17.1 (C5).

FTIR (ν_{max}, cm^{-1}): 3103 (w), 2986 (w), 1940 (w, C=C=C), 1688 (w), 1591 (w), 1489 (s), 1440 (w), 1402 (w), 1370 (w), 1235 (w), 1180 (w), 1146 (w), 1092 (s), 1062 (w), 1012 (s), 858 (w), 834 (s), 820 (s).

HRMS (ESI): calculated for $C_{14}H_{12}SCl$ $[M+H]^+$ 247.0343, found 247.0335.

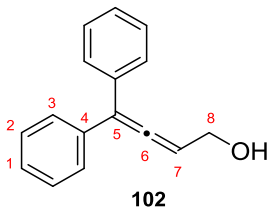
***R*$_f$** = 0.52 (hexane).



101

***tert*-Butyl (4,4-diphenylbuta-2,3-dien-1-yl)carbamate (101):** Following a modified version of the general procedure for allene formation with ketone-derived hydrazones using *N*-Boc-propargylamine (**239**) (31.0 mg, 0.2 mmol) and (diphenylmethylene)hydrazine, utilising THF instead of CH_2Cl_2 as solvent for the diazo generation and with pumping of the diazo compound over 8 min (2.0 equiv. with respect to hydrazone), purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) provided the title compound as a yellow oil (55.8 mg, 0.174 mmol, 87%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 8 H, H2 and H3), 7.31 – 7.26 (m, 2 H, H1), 5.75 (t, *J* = 5.2 Hz, 1 H, H7), 4.73 (br s, 1 H, NH), 3.90 (br s, 2 H, H8), 1.41 (s, 9 H, H11).
^{13}C NMR (150 MHz, $CDCl_3$): δ 204.8 (C6), 155.8 (C9), 136.5 (C4), 128.6 (C2/C3), 128.5 (C2/C3), 127.6 (C1), 112.7 (C5), 93.0 (C7), 79.7 (C10), 39.4 (C8), 28.5 (C11).
FTIR (ν_{max}, cm^{-1}): 3348 (br w, NH), 2976 (w), 2931 (w), 1946 (w, C=C=C), 1693 (s, C=O), 1598 (w), 1492 (s), 1453 (m), 1391 (w), 1366 (m), 1340 (w), 1273 (w), 1247 (m), 1166 (s), 1074 (w), 1051 (w), 1031 (w), 921 (w), 862 (w).
HRMS (ESI): calculated for $C_{21}H_{23}NO_2Na$ $[M+Na]^+$ 344.1621, found 344.1612.
***R*$_f$** = 0.37 (15% EtOAc/hexane).



102

4,4-Diphenylbuta-2,3-dien-1-ol (102): Following a modified version of the general procedure for allene formation with ketone-derived hydrazones using propargyl alcohol (**64**) (11.2 mg, 0.2 mmol) and (diphenylmethylene)hydrazine, utilising THF instead of CH_2Cl_2 as solvent for the diazo generation and with pumping of the diazo compound over 8 min (2.0 equiv. with respect to hydrazone), purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a yellow oil (35.7 mg, 0.161 mmol, 80%). Data are consistent with a reported example.[194]

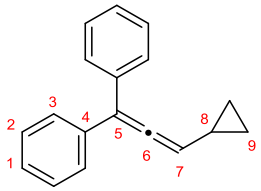
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 8 H, H2 and H3), 7.32 – 7.28 (m, 2 H, H1), 5.91 (t, *J* = 5.8 Hz, 1 H, H7), 4.32 (d, *J* = 5.8 Hz, 2 H, H8), 1.64 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.5 (C6), 136.5 (C4), 128.64 (C2/C3), 128.58 (C2/C3), 127.7 (C1), 112.7 (C5), 95.3 (C7), 60.8 (C8).

FTIR (ν_{max}, cm^{-1}): 3326 (br m, OH), 3057 (w), 2869 (w), 1942 (w, C=C=C), 1597 (m), 1492 (s), 1452 (m), 1443 (m), 1075 (m), 1013 (s), 923 (w), 902 (w).

HRMS (ESI): calculated for $C_{16}H_{15}O$ $[M+H]^+$ 223.1117, found 223.1109.

R_f = 0.30 (25% EtOAc/hexane).



103

(3-Cyclopropylpropa-1,2-diene-1,1-diyl)dibenzene (103): Following a modified version of the general procedure for allene formation with ketone-derived hydrazones using cyclopropylacetylene (**106**) (13.2 mg, 0.2 mmol) and (diphenylmethylene)hydrazine, utilising THF instead of CH_2Cl_2 as solvent for the diazo generation and with pumping of the diazo compound over 8 min (2.0 equiv. with respect to hydrazone), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a yellow oil (36.2 mg, 0.156 mmol, 78%).

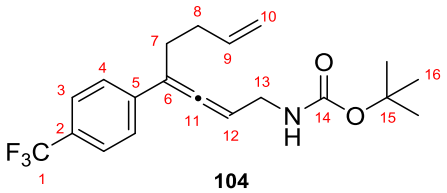
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 8 H, H2 and H3), 7.29 – 7.26 (m, 2 H, H1), 5.56 (d, *J* = 7.6 Hz, 1 H, H7), 1.48 – 1.38 (m, 1 H, H8), 0.84 – 0.75 (m, 2 H, H9a), 0.53 – 0.45 (m, 2 H, H9b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.4 (C6), 137.3 (C4), 128.54 (C2/C3), 128.46 (C2/C3), 127.2 (C1), 111.4 (C5), 99.0 (C7), 9.9 (C8), 7.2 (C9).

FTIR (ν_{max}, cm^{-1}): 3080 (w), 3057 (w), 3005 (w), 1943 (w, C=C=C), 1662 (w), 1597 (m), 1492 (s), 1443 (m), 1277 (w), 1177 (w), 1156 (w), 1073 (w), 1048 (w), 1020 (m), 965 (w), 937 (m), 921 (w), 901 (m), 850 (w), 807 (w).

HRMS (ESI): calculated for $C_{18}H_{17}$ $[M+H]^+$ 233.1325, found 233.1317.

R_f = 0.25 (hexane).



104

***tert*-Butyl (4-(4-(trifluoromethyl)phenyl)octa-2,3,7-trien-1-yl)carbamate (104):** Following the general procedure for allene formation with ketone-derived hydrazones using *N*-Boc-propargylamine (**239**) (31.0 mg, 0.2 mmol) and (1-(4-(trifluoromethyl)phenyl)pent-4-en-1-ylidene)hydrazine, purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) provided the title compound as a colourless oil (42.4 mg, 0.115 mmol, 58%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.2 Hz, 2 H, H3), 7.49 (d, *J* = 8.2 Hz, 2 H, H4), 5.88 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1 H, H9), 5.67 – 5.62 (m, 1 H, H12), 5.09 – 5.01 (m, 2 H, $H10_{cis}$ and $H10_{trans}$), 4.72 (br s, 1 H, NH), 3.88 (dt, *J* = 15.7, 5.5 Hz, 1 H, H13a/H13b), 3.79 (dt, *J* = 15.7, 5.5 Hz, 1 H, H13a/H13b), 2.61 – 2.48 (m, 2 H, H7), 2.33 – 2.28 (m, 2 H, H8), 1.40 (s, 9 H, H16).

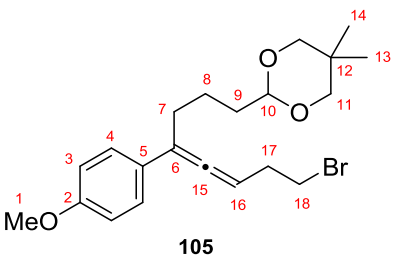
^{13}C NMR (150 MHz, $CDCl_3$): δ 203.9 (C11), 155.8 (C14), 140.4 (C5), 137.9 (C9), 129.0 (q, *J* = 32.4 Hz, C2), 126.4 (C4), 125.4 (q, *J* = 3.8 Hz, C3), 124.4 (q, *J* = 271.7 Hz, C1), 115.5 (C10), 107.6 (C6), 94.2 (C12), 79.7 (C15), 39.2 (C13), 31.9 (C8), 29.2 (C7), 28.5 (C16).

^{19}F NMR (376 MHz, $CDCl_3$): -62.5 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 3351 (br w, NH), 2979 (w), 2931 (w), 1949 (w, C=C=C), 1694 (m, C=O), 1616 (w), 1504 (m), 1422 (w), 1393 (w), 1367 (w), 1325 (s), 1277 (w), 1249 (m), 1164 (s), 1123 (s), 1069 (m), 1015 (w), 914 (w), 845 (w).

HRMS (ESI): calculated for $C_{20}H_{24}F_3NO_2Na$ $[M+Na]^+$ 390.1651, found 390.1641.

***R*$_f$** = 0.42 (15% EtOAc/hexane).



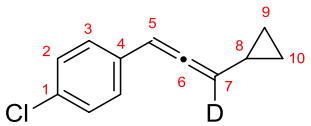
105

2-(8-Bromo-4-(4-methoxyphenyl)octa-4,5-dien-1-yl)-5,5-dimethyl-1,3-dioxane (105): Following the general procedure for allene formation with ketone-derived hydrazones using 4-bromo-1-butyne (26.6 mg, 0.2 mmol) and (4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-methoxyphenyl)butylidene)hydrazine, purified by silica gel column chromatography (eluent:

5% → 10% Et_2O/hexane) provided the title compound as a yellow oil (45.3 mg, 0.111 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.8 Hz, 2 H, H4), 6.85 (d, *J* = 8.8 Hz, 2 H, H3), 5.54 – 5.47 (m, 1 H, H16), 4.44 (t, *J* = 4.7 Hz, 1 H, H10), 3.80 (s, 3 H, H1), 3.60 (d, *J* = 10.9 Hz, 2 H, H11a/H11b), 3.46 (t, *J* = 7.1 Hz, 2 H, H18), 3.41 (d, *J* = 10.9 Hz, 2 H, H11a/H11b), 2.65 (q, *J* = 7.1 Hz, 2 H, H17), 2.46 – 2.39 (m, 2 H, H7), 1.77 – 1.62 (m, 4 H, H8 and H9), 1.19 (s, 3 H, H13/H14), 0.71 (s, 3 H, H13/H14).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (C15), 158.7 (C2), 128.9 (C5), 127.3 (C4), 114.0 (C3), 106.4 (C6), 102.2 (C10), 92.0 (C16), 77.4 (C11), 55.4 (C1), 34.7 (C7), 32.9 (C17), 32.3 (C18), 30.3 (C9), 30.0 (C12), 23.2 (C13/C14), 22.6 (C8), 22.0 (C13/C14).
FTIR (ν_{max}, cm^{-1}): 2953 (m), 2836 (w), 1943 (w, C=C=C), 1607 (m), 1578 (w), 1510 (s), 1464 (m), 1394 (m), 1363 (w), 1292 (m), 1248 (s), 1177 (m), 1131 (s), 1097 (m), 1037 (m), 970 (w), 924 (w), 886 (w), 833 (w).
HRMS (ESI): calculated for $C_{21}H_{30}O_3Br$ $[M+H]^+$ 409.1373, found 409.1362.
R_f = 0.31 (15% Et_2O/hexane).

5.2.4. Deuteration experiment



74-*d*

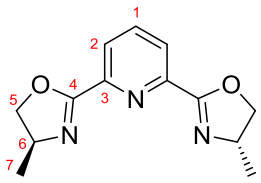
1-Chloro-4-(3-cyclopropylpropa-1,2-dien-1-yl-3-*d*)benzene (74-*d*): Following a modified version of the general procedure for allene formation with aldehyde-derived hydrazones using cyclopropylacetylene (**106**) (13.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), with CD_3OD (25 µL, 0.6 mmol, 3.0 equiv.) being added to the mixture of alkyne, Et_3N and 1,4-dioxane prior to pre-mixing for 10 min. Purification by silica gel column chromatography (eluent: hexane) provided the title compound as a 37:63 mixture of allenes **74-*d*** and **74** as a colourless oil (35.5 mg, 0.186 mmol, combined yield 93%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2 H, H2), 7.21 (d, *J* = 8.6 Hz, 2 H, H3), 6.20 – 6.13 (m, 1 H, H5), 5.44 (dd, *J* = 7.5, 6.6 Hz, 0.63 H, H7 of **74**), 1.44 – 1.28 (m, 1 H, H8), 0.81 – 0.73 (m, 2 H, H9a and H10a), 0.50 – 0.40 (m, 2 H, H9b and H10b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 205.0 (C6), 133.6 (C1), 132.4 (C4), 128.8 (C2), 127.9 (C3), 100.1 (C7), 95.5 (C5 of **74-*d***), 95.4 (C5 of **74**), 9.6 (C8 of **74**), 9.5 (C8 of **74-*d***), 7.21 (C9/C10 of **74**), 7.19 (C9/C10 of **74-*d***), 7.12 (C9/C10 of **74**), 7.10 (C9/C10 of **74-*d***).
HRMS (ESI): calculated for $C_{12}H_{11}DCl$ $[M+H]^+$ 192.0685, found 192.0677.
***R*$_f$** = 0.60 (hexane).

5.3. Experimental data for Chapter 3

5.3.1. Synthetic procedures and characterisation for PyBOX ligands

General procedure for PyBOX synthesis: A solution of the appropriate 2,6-pyridinedicarbonitrile (1.0 mmol, 1 equiv.), the appropriate amino alcohol (2.0 mmol, 2 equiv.) and zinc(II) triflate (36 mg, 0.1 mmol, 0.1 equiv.) in toluene (15 mL) was heated under reflux for 48 h. The reaction mixture was then cooled to r.t. and diluted with EtOAc (10 mL). The organic layer was washed with brine (3 × 25 mL), saturated aqueous $NaHCO_3$ solution (3 × 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was further purified by silica gel column chromatography or recrystallisation as appropriate.



156

2,6-Bis((*S*)-4-methyl-4,5-dihydrooxazol-2-yl)pyridine (156): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (*S*)-2-aminopropan-1-ol (0.286 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a white amorphous solid (0.022 g, 0.09 mmol, 9%), m.p. 148-151 °C (lit. m.p.[195] 163.0-165.5 °C, on material with 0.25 mol H_2O). Data are consistent with a reported example.[195]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.8 Hz, 2 H, H2), 7.86 (t, *J* = 7.8 Hz, 1 H, H1), 4.61 (dd, *J* = 9.5, 8.3 Hz, 2 H, H5a), 4.43 (ddq, *J* = 9.5, 8.3, 6.7 Hz, 2 H, H6), 4.07 (t, *J* = 8.3 Hz, 2 H, H5b), 1.37 (d, *J* = 6.7 Hz, 6 H, H7).

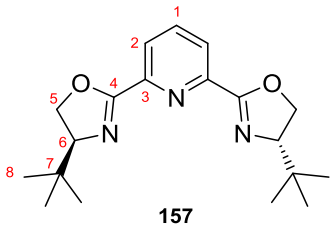
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.4 (C4), 147.0 (C3), 137.4 (C1), 125.8 (C2), 74.9 (C5), 62.4 (C6), 21.5 (C7).

FTIR (ν_{max}, cm^{-1}): 2971 (m), 2900 (w), 1641 (s), 1575 (s), 1531 (w), 1459 (m), 1385 (m), 1305 (w), 1269 (w), 1246 (w), 1171 (w), 1119 (m), 1068 (s), 973 (s), 945 (m), 831 (w).

HRMS (ESI): calculated for $C_{13}H_{16}N_3O_2$ $[M+H]^+$ 246.1237, found 246.1231.

R_f = 0.26 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.3}$ = -127.6 ($CHCl_3$, *c* = 0.5); lit.[195] $[\alpha]_D$ = -131.8 ($CHCl_3$, *c* = 0.72).



157

2,6-Bis((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)pyridine (157): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.387 g, 3.0 mmol, 1 equiv.) and L-*tert*-leucinol (**205**) (0.703 g, 6.0 mmol, 2 equiv.), after extraction and evaporation provided the title compound as a white crystalline solid (0.970 g, 2.9 mmol, 98%), m.p. 236-238 °C. Data are consistent with a reported example.[196]

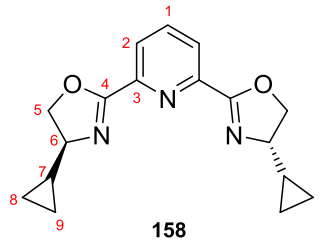
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 7.8 Hz, 2 H, H2), 7.84 (t, *J* = 7.8 Hz, 1 H, H1), 4.47 (dd, *J* = 10.3, 8.6 Hz, 2 H, H5a), 4.32 (t, *J* = 8.6 Hz, 2 H, H6), 4.10 (dd, *J* = 10.3, 8.6 Hz, 2 H, H5b), 0.96 (s, 18 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.3 (C4), 147.1 (C3), 137.2 (C1), 126.0 (C2), 76.5 (C6), 69.6 (C5), 34.1 (C7), 26.1 (C8).

FTIR (ν_{max}, cm^{-1}): 2957 (m), 2902 (w), 2869 (w), 1641 (s), 1590 (w), 1569 (m), 1475 (m), 1459 (m), 1417 (w), 1395 (m), 1377 (s), 1363 (s), 1319 (w), 1276 (m), 1212 (m), 1195 (w), 1153 (w), 1106 (s), 1075 (m), 1057 (m), 1032 (m), 997 (m), 967 (m), 956 (m), 931 (m), 899 (w), 865 (w), 841 (m), 757 (m).

HRMS (ESI): calculated for $C_{19}H_{27}N_3O_2Na$ $[M+Na]^+$ 352.1995, found 352.2005.

$[\alpha]_D^{24.0}$ = -115.0 (CH_2Cl_2, *c* = 1.0); lit.[196] $[\alpha]_D^{27}$ = -118 (CH_2Cl_2, *c* = 0.5).



158

2,6-Bis((*S*)-4-cyclopropyl-4,5-dihydrooxazol-2-yl)pyridine (158): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (*S*)-2-amino-2-cyclopropylethan-1-ol (0.202 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 30% acetone/CH_2Cl_2) provided the title compound as a yellow amorphous solid (0.096 g, 0.32 mmol, 32%), m.p. 82-85 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.8 Hz, 2 H, H2), 7.85 (t, *J* = 7.8 Hz, 1 H, H1), 4.60 (dd, *J* = 9.8, 8.3 Hz, 2 H, H5a), 4.28 (t, *J* = 8.3 Hz, 2 H, H5b), 3.82 (dt, *J* = 9.8, 8.3 Hz, 2 H, H6), 1.01 – 0.94 (m, 2 H, H7), 0.66 – 0.60 (m, 2 H, H8/H9), 0.57 – 0.51 (m, 2 H, H8/H9), 0.49 – 0.44 (m, 2 H, H8/H9), 0.36 – 0.31 (m, 2 H, H8/H9).

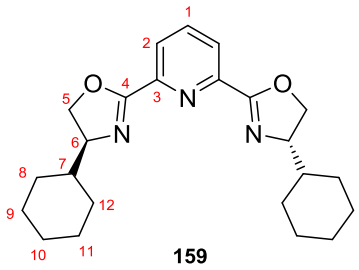
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.9 (C4), 147.0 (C3), 137.3 (C1), 126.0 (C2), 73.4 (C5), 71.3 (C6), 16.0 (C7), 3.3 (C8/C9), 2.3 (C8/C9).

FTIR (ν_{max}, cm^{-1}): 3403 (w), 3084 (w), 3007 (w), 2900 (w), 1647 (m), 1573 (m), 1533 (w), 1447 (w), 1380 (m), 1355 (m), 1331 (m), 1250 (m), 1205 (w), 1170 (m), 1147 (w), 1106 (w), 1083 (w), 1062 (m), 1051 (m), 1025 (m), 973 (s), 939 (m), 895 (m), 828 (s), 819 (s).

HRMS (ESI): calculated for $C_{17}H_{20}N_3O_2$ $[M+H]^+$ 298.1550, found 298.1556.

R_f = 0.43 (30% acetone/CH_2Cl_2).

$[\alpha]_D^{28.3}$ = -189.4 ($CHCl_3$, *c* = 1.0).



159

2,6-Bis((*S*)-4-cyclohexyl-4,5-dihydrooxazol-2-yl)pyridine (159): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (*S*)-2-amino-2-cyclohexylethan-1-ol (0.286 g, 2.0 mmol, 2 equiv.), purified by recrystallisation from EtOAc provided the title compound as a white flaky solid (0.123 g, 0.32 mmol, 32%), m.p. 204-206 °C. Compound has been prepared previously,[197] but NMR spectra were recorded in CD_2Cl_2.

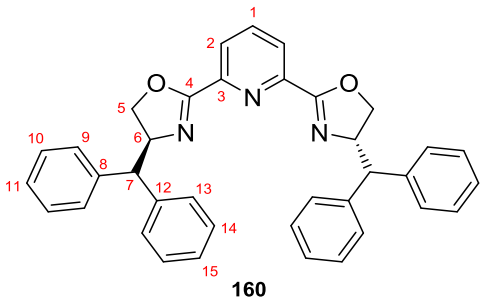
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, *J* = 7.9 Hz, 2 H, H2), 7.84 (t, *J* = 7.9 Hz, 1 H, H1), 4.51 (dd, *J* = 9.7, 8.5 Hz, 2 H, H5a), 4.24 (t, *J* = 8.5 Hz, 2H, H5b), 4.13 (ddd, *J* = 9.7, 8.5, 7.0 Hz, 2 H, H6), 2.00 (br d, *J* = 12.8 Hz, 2 H, H8a/H12a), 1.80 – 1.72 (m, 4 H, H9a and H11a), 1.68 (br d, *J* = 12.1 Hz, 2 H, H10a), 1.61 (br d, *J* = 12.6 Hz, 2 H, H8a/H12a), 1.57 – 1.49 (m, 2 H, H7), 1.32 – 1.16 (m, 6 H, H9b, H10b and H11b), 1.13 – 1.01 (m, 4 H, H8b and H12b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.3 (C4), 147.1 (C3), 137.3 (C1), 125.8 (C2), 72.2 (C6), 71.3 (C5), 43.0 (C7), 29.8 (C8/C12), 29.1 (C8/C12), 26.6 (C10), 26.2 (C9 and C11).

FTIR (ν_{max}, cm^{-1}): 2919 (m), 2850 (m), 1629 (s), 1569 (w), 1451 (w), 1414 (w), 1379 (s), 1326 (w), 1282 (w), 1228 (w), 1101 (s), 1072 (s), 1057 (w), 998 (w), 980 (w), 962 (s), 941 (w), 910 (w), 885 (w), 843 (w), 756 (w).

HRMS (ESI): calculated for $C_{23}H_{32}N_3O_2$ $[M+H]^+$ 382.2489, found 382.2498.

$[\alpha]_D^{28.3}$ = -162.8 ($CHCl_3$, *c* = 1.0).



160

2,6-Bis((*S*)-4-benzhydryl-4,5-dihydrooxazol-2-yl)pyridine (160): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (*S*)-2-amino-3,3-diphenylpropan-1-ol (0.455 g, 2.0 mmol, 2 equiv.), purified by recrystallisation from toluene and washed on the filter with cold EtOAc (2 mL) provided the title compound as an off-white flaky solid (0.195 g, 0.35 mmol, 35%), m.p. 262-264 °C.

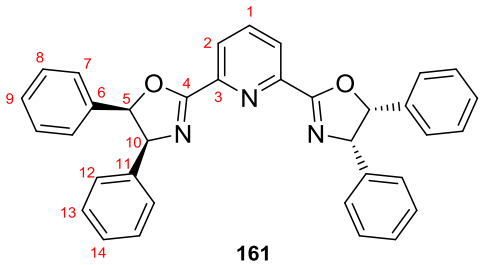
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.9 Hz, 2 H, H2), 7.78 (t, *J* = 7.9 Hz, 1 H, H1), 7.37 – 7.13 (m, 20 H, ArH), 5.17 (td, *J* = 9.3, 8.5 Hz, 2 H, H6), 4.54 (appears t, *J* = 9.3 Hz, 2 H, H5a), 4.20 (appears t, *J* = 8.5 Hz, 2 H, H5b), 4.07 (d, *J* = 9.3 Hz, 2 H, H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 163.0 (C4), 146.9 (C3), 142.2 (C8/C12), 142.0 (C8/C12), 137.2 (C1), 128.9 (ArCH), 128.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.0 (C11/C15), 126.6 (C11/C15), 126.3 (C2), 72.3 (C5), 70.5 (C6), 57.1 (C7).

FTIR (ν_{max}, cm^{-1}): 1638 (m), 1571 (w), 1495 (w), 1452 (w), 1379 (s), 1276 (w), 1108 (s), 1073 (m), 1031 (w), 975 (w), 830 (w).

HRMS (ESI): calculated for $C_{37}H_{32}N_3O_2$ $[M+H]^+$ 550.2489, found 550.2506.

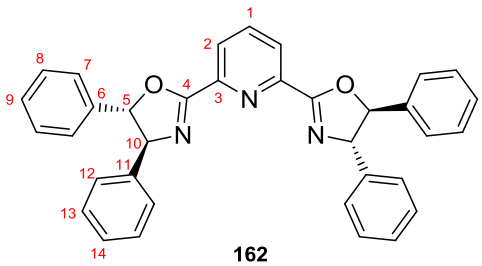
$[\alpha]_D^{28.3}$ = -93.1 ($CHCl_3$, *c* = 1.0).



161

2,6-Bis((4*S*,5*R*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (161): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (1*R*,2*S*)-2-amino-1,2-diphenylethan-1-ol (0.427 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 2% MeOH/CH_2Cl_2) and then recrystallisation from CH_2Cl_2/hexane provided the title compound as a white crystalline solid (0.091 g, 0.18 mmol, 18%), m.p. 233-236 °C (lit. m.p.[198] 225-226 °C). Data are consistent with a reported example.[198]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (d, *J* = 7.9 Hz, 2 H, H2), 8.04 (t, *J* = 7.9 Hz, 1 H, H1), 7.08 – 6.95 (m, 20 H, ArH), 6.14 (d, *J* = 10.3 Hz, 2 H, H5), 5.83 (d, *J* = 10.3 Hz, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 164.1 (C4), 147.2 (C3), 137.8 (C1), 137.3 (C6/C11), 136.1 (C6/C11), 128.0 (C7/C8/C12/C13), 127.81 (C7/C8/C12/C13), 127.76 (C7/C8/C12/C13), 127.6 (C9/C14), 127.2 (C9/C14), 126.7 (C7/C8/C12/C13), 126.6 (C2), 86.4 (C5), 74.5 (C10).
FTIR (ν_{max}, cm^{-1}): 1664 (w), 1630 (m), 1572 (m), 1495 (w), 1453 (m), 1357 (w), 1321 (m), 1261 (w), 1244 (w), 1211 (w), 1169 (m), 1141 (m), 1108 (m), 1077 (s), 1028 (w), 995 (w), 968 (s), 921 (m), 888 (w), 859 (w), 821 (m), 765 (s).
HRMS (ESI): calculated for $C_{35}H_{28}N_3O_2$ $[M+H]^+$ 522.2176, found 522.2181.
R_f = 0.18 (2% MeOH/CH_2Cl_2).
$[\alpha]_D^{28.3}$ = -293.7 ($CHCl_3$, *c* = 1.0); lit.[198] $[\alpha]_D$ = -305 ($CHCl_3$, *c* = 0.5).

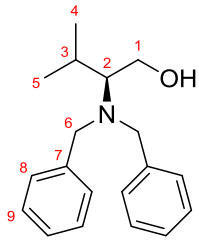


162

2,6-Bis((4*S*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (162): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (1*S*,2*S*)-2-amino-1,2-diphenylethan-1-ol (0.427 g, 2.0 mmol, 2 equiv.), purified

by silica gel column chromatography (eluent: 2% MeOH/CH_2Cl_2) provided the title compound as a white amorphous solid (0.088 g, 0.17 mmol, 17%), m.p. 200-201 °C (lit. m.p.[199] 201-202 °C). Data are consistent with a reported example.[199]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (d, *J* = 7.9 Hz, 2 H, H2), 7.98 (t, *J* = 7.9 Hz, 1 H, H1), 7.41 – 7.30 (m, 20 H, ArH), 5.56 (d, *J* = 8.4 Hz, 2 H, H5), 5.35 (d, *J* = 8.4 Hz, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 163.0 (C4), 147.1 (C3), 141.3 (C6/C11), 139.8 (C6/C11), 137.5 (C1), 128.9 (C7/C8/C12/C13), 128.9 (C7/C8/C12/C13), 128.6 (C9/C14), 127.9 (C9/C14), 126.9 (C7/C8/C12/C13), 126.7 (C2), 126.3 (C7/C8/C12/C13), 90.1 (C5), 79.1 (C10).
FTIR (ν_{max}, cm^{-1}): 1648 (m), 1600 (w), 1568 (m), 1493 (w), 1448 (m), 1341 (w), 1288 (m), 1258 (m), 1222 (w), 1162 (m), 1123 (m), 1080 (m), 1025 (w), 1012 (w), 978 (s), 956 (s), 915 (w), 890 (w), 846 (m), 758 (s).
HRMS (ESI): calculated for $C_{35}H_{27}N_3O_2Na$ $[M+Na]^+$ 544.1995, found 544.2006.
R_f = 0.26 (2% MeOH/CH_2Cl_2).
$[\alpha]_D^{28.3}$ = -37.8 ($CHCl_3$, *c* = 1.0); lit.[199] $[\alpha]_D^{20}$ = -41.4 ($CHCl_3$, *c* = 0.5).



168

(*S*)-2-(Dibenzylamino)-3-methylbutan-1-ol (168): A mixture of L-valinol (**167**) (2.06 g, 20.0 mmol, 1 equiv.), benzyl bromide (5.24 mL, 44.0 mmol, 2.2 equiv.), potassium carbonate (8.30 g, 60.0 mmol, 3 equiv.) and tetrabutylammonium iodide (2.22 g, 6.0 mmol, 0.3 equiv.) in acetonitrile (200 mL) was heated under reflux for 16 h. The solvent was removed under reduced pressure and the residue diluted with EtOAc (300 mL) and water (300 mL). The organic layer was separated and the aqueous layer extracted further with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was then purified by silica gel column chromatography (eluent: 15% EtOAc/hexane) to provide the title compound as a colourless oil (4.75 g, 16.8 mmol, 84%). Data are consistent with a reported example.[200]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 4 H, H9), 7.26 – 7.22 (m, 6 H, H8 and H10), 3.89 (d, *J* = 13.2 Hz, 2 H, H6a), 3.69 (d, *J* = 13.2 Hz, 2 H, H6b), 3.57 (dd, *J* = 10.7, 4.6 Hz, 1 H, H1a), 3.44 (dd, *J* = 10.7, 9.8 Hz, 1 H, H1b), 2.95 (br s, 1 H, OH), 2.54 (ddd, *J* = 9.8, 7.8, 4.6 Hz, 1 H, H2), 2.12 – 2.01 (m, 1 H, H3), 1.14 (d, *J* = 6.8 Hz, 3 H, H4/H5), 0.89 (d, *J* = 6.7 Hz, 3 H, H4/H5).

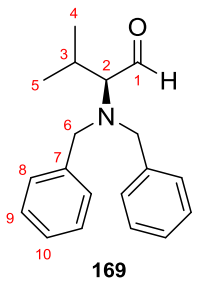
^{13}C NMR (150 MHz, $CDCl_3$): δ 139.8 (C7), 129.4 (C8), 128.6 (C9), 127.3 (C10), 64.8 (C2), 59.4 (C1), 54.4 (C6), 27.7 (C3), 22.9 (C4/C5), 20.3 (C4/C5).

FTIR (ν_{max}, cm^{-1}): 3443 (br w, OH), 3064 (w), 3028 (w), 2956 (m), 2871 (m), 1703 (w), 1603 (w), 1494 (m), 1453 (s), 1362 (m), 1322 (w), 1247 (w), 1206 (w), 1137 (w), 1099 (m), 1064 (s), 1028 (s), 1009 (s), 910 (m), 858 (w), 827 (w), 787 (w).

HRMS (ESI): calculated for $C_{19}H_{26}NO$ $[M+H]^+$ 284.2009, found 284.2011.

R_f = 0.28 (15% EtOAc/hexane).

$[\alpha]_D^{27.7}$ = +23.1 ($CHCl_3$, *c* = 1.0); lit.[200] $[\alpha]_D^{20}$ = +24.5 ($CHCl_3$, *c* = 0.8).



169

(*S*)-2-(Dibenzylamino)-3-methylbutanal (169): To a solution of oxalyl chloride (1.92 mL, 22.5 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (20 mL) at -78 °C was added slowly dropwise a solution of DMSO (2.34 mL, 33.0 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (20 mL), keeping the internal temperature below -60 °C. The mixture was stirred further for 5 min. A solution of (*S*)-2-(dibenzylamino)-3-methylbutan-1-ol (**168**) (4.25 g, 15.0 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was added slowly dropwise and stirred further for 15 min. Triethylamine (10.4 mL, 75.0 mmol, 5 equiv.) was then added, stirred at -78 °C for 30 min, warmed to r.t. and quenched with water (75 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 5% EtOAc/hexane) to provide the title compound as a pale yellow turbid oil (3.71 g, 13.2 mmol, 88%). Data are consistent with a reported example.[201]

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.86 (d, *J* = 3.4 Hz, 1 H, H1), 7.37 (d, *J* = 7.3 Hz, 4 H, H8), 7.33 (t, *J* = 7.3 Hz, 4 H, H9), 7.26 (t, *J* = 7.3 Hz, 2 H, H10), 4.03 (d, *J* = 13.8 Hz, 2 H, H6a), 3.72 (d, *J* = 13.8 Hz, 2 H, H6b), 2.73 (dd, *J* = 10.0, 3.4 Hz, 1 H, H2), 2.29 (d sept, *J* = 10.0, 6.7 Hz, 1 H, H3), 1.09 (d, *J* = 6.7 Hz, 3 H, H4/H5), 0.88 (d, *J* = 6.7 Hz, 3 H, H4/H5).

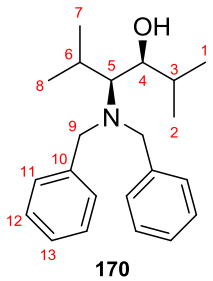
^{13}C NMR (150 MHz, $CDCl_3$): δ 205.3 (C1), 139.4 (C7), 128.9 (C8), 128.5 (C9), 127.3 (C10), 71.7 (C2), 54.7 (C6), 26.2 (C3), 20.3 (C4/C5), 20.0 (C4/C5).

FTIR (ν_{max}, cm^{-1}): 3063 (w), 3030 (w), 2960 (w), 2809 (w), 2716 (w), 1716 (s, C=O), 1602 (w), 1494 (m), 1454 (m), 1368 (w), 1308 (w), 1241 (w), 1208 (w), 1155 (w), 1112 (w), 1091 (w), 1074 (m), 1049 (w), 1028 (m), 971 (w), 908 (w), 846 (w), 824 (w).

HRMS (ESI): calculated for $C_{19}H_{24}NO$ $[M+H]^+$ 282.1852, found 282.1850.

R_f = 0.36 (5% EtOAc/hexane).

$[\alpha]_D^{23.7}$ = -63.4 ($CHCl_3$, *c* = 1.0); lit.[201] $[\alpha]_D^{25}$ = -62.2 ($CHCl_3$, *c* = 1.0).



170

(3*S*,4*S*)-4-(Dibenzylamino)-2,5-dimethylhexan-3-ol (170): To a solution of (*S*)-2-(dibenzylamino)-3-methylbutanal (**169**) (2.81 g, 10.0 mmol, 1 equiv.) in anhydrous toluene (40 mL) was added a solution of diisopropylzinc (30 mL, 1.0 M in toluene, 30.0 mmol, 3 equiv.) at 0 °C and the reaction mixture stirred further for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 5% EtOAc/hexane) to provide the title compound as a yellow oil (3.08 g, 9.46 mmol, 95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 4 H, H12), 7.27 (d, *J* = 7.0 Hz, 4 H, H11), 7.26 – 7.21 (m, 2 H, H13), 4.60 (br s, 1 H, OH), 3.93 (d, *J* = 13.0 Hz, 2 H, H9a), 3.66 (dd, *J* = 9.9, 1.5 Hz, 1 H, H4), 3.42 (d, *J* = 13.0 Hz, 2 H, H9b), 2.51 (dd, *J* = 9.9, 2.2 Hz, 1 H, H5), 2.24 (sept d, *J* = 7.4, 2.2 Hz, 1 H, H6), 1.60 (sept d, *J* = 6.7, 1.5 Hz, 1 H, H3), 1.04 (m, 9 H, H1/H2, H7 and H8), 0.44 (d, *J* = 6.7 Hz, 3 H, H1/H2).

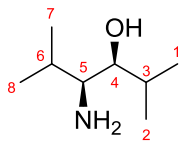
^{13}C NMR (150 MHz, $CDCl_3$): δ 139.0 (C10), 129.4 (C11), 128.5 (C12), 127.3 (C13), 70.5 (C4), 61.9 (C5), 53.8 (C9), 30.0 (C3), 25.0 (C6), 23.9 (C1/C2/C7/C8), 21.7 (C1/C2/C7/C8), 19.3 (C1/C2/C7/C8), 13.5 (C1/C2).

FTIR (ν_{max}, cm^{-1}): 3354 (br w, OH), 3064 (w), 3029 (w), 2959 (s), 2874 (m), 1604 (w), 1495 (m), 1454 (s), 1414 (w), 1389 (m), 1362 (m), 1241 (w), 1208 (w), 1179 (w), 1137 (w), 1095 (m), 1072 (s), 1028 (m), 1005 (s), 972 (s), 947 (m), 911 (w), 867 (w), 847 (w), 810 (w).

HRMS (ESI): calculated for $C_{22}H_{32}NO$ $[M+H]^+$ 326.2478, found 326.2483.

R_f = 0.28 (5% EtOAc/hexane).

$[\alpha]_D^{26.0}$ = +21.0 ($CHCl_3$, *c* = 1.0).



171

(3*S*,4*S*)-4-Amino-2,5-dimethylhexan-3-ol (171): A mixture of (3*S*,4*S*)-4-(dibenzylamino)-2,5-dimethylhexan-3-ol (**170**) (1.63 g, 5.0 mmol, 1 equiv.), 20% palladium(II) hydroxide on carbon (0.5 g) and acetic acid (0.34 mL, 6.0 mmol, 1.2 equiv.) in ethanol (50 mL) was stirred under H_2 (balloon) at 50 °C for 16 h. A further portion of 20% palladium(II) hydroxide on carbon (0.5 g) was added, then stirred under H_2 (balloon) at 50 °C for a further 16 h. The mixture was filtered through a pad of Celite, eluting with ethanol, and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and 1 M aqueous NaOH solution (25 mL) was added. The organic layer was separated and the aqueous layer extracted further with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to provide the title compound as a white amorphous solid (0.486 g, 3.3 mmol, 67%), m.p. 55-57 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.15 (t, *J* = 5.3 Hz, 1 H, H4), 2.52 (t, *J* = 5.3 Hz, 1 H, H5), 1.81 (br s, 3 H, NH_2 and OH), 1.76 (sept d, *J* = 6.8, 5.3 Hz, 1 H, H6), 1.69 (sept d, *J* = 6.8, 5.3 Hz, 1 H, H3), 0.95 (d, *J* = 6.8 Hz, 3 H, H1/H2), 0.94 (d, *J* = 6.8 Hz, 3 H, H7/H8), 0.91 (d, *J* = 6.8 Hz, 3 H, H1/H2), 0.86 (d, *J* = 6.8 Hz, 3 H, H7/H8).

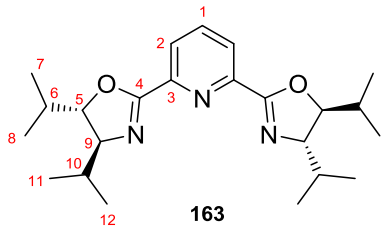
^{13}C NMR (150 MHz, $CDCl_3$): δ 75.7 (C4), 57.7 (C5), 30.8 (C3), 30.0 (C6), 20.4 (C7/C8), 20.0 (C1/C2), 16.91 (C1/C2/C7/C8), 16.86 (C1/C2/C7/C8).

FTIR (ν_{max}, cm^{-1}): 3348 (w, NH_2), 3300 (w, NH_2), 3165 (br w, OH), 2962 (m), 2932 (m), 2910 (m), 2874 (m), 1619 (m), 1585 (w), 1470 (m), 1389 (w), 1361 (w), 1338 (w), 1315 (w),

1299 (w), 1252 (w), 1189 (w), 1134 (m), 1113 (w), 1057 (m), 1021 (w), 1001 (s), 960 (m), 947 (m), 926 (m), 903 (s), 806 (m), 766 (m).

HRMS (ESI): calculated for $C_8H_{20}NO$ $[M+H]^+$ 146.1539, found 146.1534.

$[\alpha]_D^{25.2}$ = +6.6 ($CHCl_3$, *c* = 1.0).



163

2,6-Bis((4*S*,5*S*)-4,5-diisopropyl-4,5-dihydrooxazol-2-yl)pyridine (163): Following the general procedure for PyBOX synthesis, using 2,6-pyridinedicarbonitrile (0.129 g, 1.0 mmol, 1 equiv.) and (3*S*,4*S*)-4-amino-2,5-dimethylhexan-3-ol (0.290 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 3% MeOH/CH_2Cl_2) provided the title compound as a yellow gum (0.065 g, 0.17 mmol, 17%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.8 Hz, 2 H, H2), 7.83 (t, *J* = 7.8 Hz, 1 H, H1), 4.24 (t, *J* = 5.9 Hz, 2 H, H5), 3.82 (t, *J* = 5.9 Hz, 2 H, H9), 1.89 – 1.76 (m, 4 H, H6 and H10), 0.99 – 0.94 (m, 24 H, H7, H8, H11 and H12).

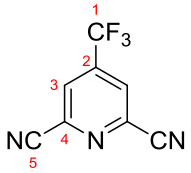
^{13}C NMR (150 MHz, $CDCl_3$): δ 161.7 (C4), 147.2 (C3), 137.3 (C1), 125.5 (C2), 87.9 (C5), 74.9 (C9), 32.9 (C6/C10), 32.7 (C6/C10), 18.8 (C7/C8/C11/C12), 18.4 (C7/C8/C11/C12), 17.9 (C7/C8/C11/C12), 17.3 (C7/C8/C11/C12).

FTIR (ν_{max}, cm^{-1}): 2961 (s), 2933 (m), 2875 (m), 1666 (m), 1575 (m), 1523 (w), 1465 (s), 1386 (m), 1370 (m), 1261 (m), 1239 (m), 1170 (m), 1108 (m), 1079 (m), 979 (s), 955 (m), 929 (w), 904 (w), 832 (w), 763 (w).

HRMS (ESI): calculated for $C_{23}H_{36}N_3O_2$ $[M+H]^+$ 386.2802, found 386.2803.

R_f = 0.34 (3% MeOH/CH_2Cl_2).

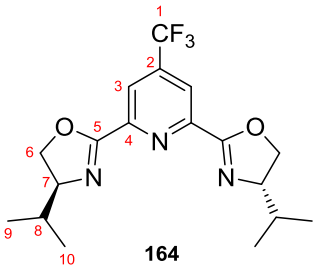
$[\alpha]_D^{28.4}$ = -93.2 ($CHCl_3$, *c* = 1.0).



172

4-(Trifluoromethyl)pyridine-2,6-dicarbonitrile (172): To a 20 mL microwave vial was added 2,6-dichloro-4-(trifluoromethyl)pyridine (1.080 g, 5.0 mmol, 1.0 equiv.), zinc(II) cyanide (0.646 g, 5.5 mmol, 1.1 equiv.), zinc powder (65 mg, 1.0 mmol, 0.2 equiv.), palladium(II) trifluoroacetate (83 mg, 0.25 mmol, 0.05 equiv.), *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (0.199 g, 0.50 mmol, 0.1 equiv.) and anhydrous DMA (20 mL). The mixture was placed under vacuum and backfilled with argon (three cycles), stirred at r.t. for 20 min, then subsequently heated to 95 °C for 16 h. The mixture was then cooled to r.t. and filtered through a pad of Celite, eluting with EtOAc. The solvents were removed by vacuum distillation (6-10 mmHg) and the residue purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) to provide the title compound as a pale yellow amorphous solid (0.620 g, 3.1 mmol, 63%), m.p. 103-104 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (q, *J* = 0.6 Hz, 2 H, H3).
^{13}C NMR (150 MHz, $CDCl_3$): δ 142.0 (q, *J* = 36.8 Hz, C2), 136.7 (C4), 127.0 (q, *J* = 3.4 Hz, C3), 120.9 (q, *J* = 274.8 Hz, C1), 114.5 (C5).
^{19}F NMR (376 MHz, $CDCl_3$): δ -64.8 (s, 3 F, F1).
FTIR (ν_{max}, cm^{-1}): 3069 (w), 1870 (w), 1567 (w), 1416 (w), 1403 (m), 1352 (m), 1304 (w), 1250 (w), 1222 (m), 1212 (m), 1153 (s), 1105 (m), 981 (w), 925 (m), 863 (m), 792 (w).
HRMS (ESI): calculated for $C_8H_3F_3N_3$ $[M+H]^+$ 198.0274, found 198.0265.
R_f = 0.27 (10% EtOAc/hexane).

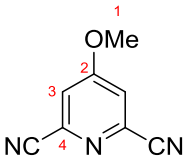


164

(4*S*,4'*S*)-2,2'-(4-(Trifluoromethyl)pyridine-2,6-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (164): Following the general procedure for PyBOX synthesis, using 4-(trifluoromethyl)pyridine-2,6-dicarbonitrile (**172**) (0.197 g, 1.0 mmol, 1 equiv.) and L-valinol

(**167**) (0.206 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 5% acetone/CH_2Cl_2) provided the title compound as an off-white amorphous solid (0.179 g, 0.48 mmol, 48%), m.p. 90-93 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (s, 2 H, H3), 4.55 (dd, *J* = 9.8, 8.5 Hz, 2 H, H6a), 4.25 (t, *J* = 8.5 Hz, 2 H, H6b), 4.16 (ddd, *J* = 9.8, 8.5, 6.7 Hz, 2 H, H7), 1.92 – 1.82 (oct, *J* = 6.7 Hz, 2 H, H8), 1.04 (d, *J* = 6.7 Hz, 6 H, H9/H10), 0.93 (d, *J* = 6.7 Hz, 6 H, H9/H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 161.5 (C5), 148.4 (C4), 139.9 (q, *J* = 35.0 Hz, C2), 122.3 (q, *J* = 273.7 Hz, C1), 121.6 (q, *J* = 3.5 Hz, C3), 73.2 (C7), 71.4 (C6), 32.9 (C8), 19.1 (C9/C10), 18.4 (C9/C10).
^{19}F NMR (376 MHz, $CDCl_3$): δ -64.6 (s, 3 F, F1).
FTIR (ν_{max}, cm^{-1}): 2961 (w), 2874 (w), 1670 (w), 1644 (m), 1608 (w), 1574 (w), 1467 (w), 1443 (w), 1413 (w), 1386 (w), 1368 (w), 1356 (w), 1337 (w), 1294 (m), 1277 (m), 1259 (m), 1174 (m), 1141 (s), 1112 (m), 1041 (w), 1020 (w), 978 (m), 961 (m), 938 (m), 907 (m), 819 (w), 768 (w), 753 (w).
HRMS (ESI): calculated for $C_{18}H_{23}F_3N_3O_2$ $[M+H]^+$ 370.1737, found 370.1742.
R_f = 0.29 (5% acetone/CH_2Cl_2).
$[\alpha]_D^{28.3}$ = -124.8 ($CHCl_3$, *c* = 1.0).

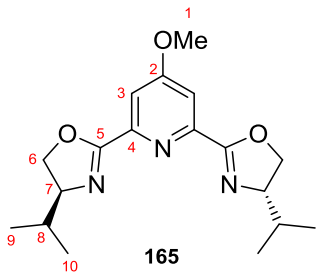


173

4-Methoxypyridine-2,6-dicarbonitrile (173): To a 20 mL microwave vial was added 2,6-dichloro-4-methoxypyridine (0.890 g, 5.0 mmol, 1.0 equiv.), zinc(II) cyanide (0.646 g, 5.5 mmol, 1.1 equiv.), zinc powder (65 mg, 1.0 mmol, 0.2 equiv.), palladium(II) trifluoroacetate (83 mg, 0.25 mmol, 0.05 equiv.), *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (0.199 g, 0.50 mmol, 0.1 equiv.) and anhydrous DMA (20 mL). The mixture was placed under vacuum and backfilled with argon three times, stirred at r.t. for 20 min, then subsequently heated to 95 °C for 16 h. The mixture was then cooled to r.t. and filtered through a pad of Celite, eluting with EtOAc. The solvents were removed by vacuum distillation (6-10 mmHg) and the residue purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) to provide the title compound as a white amorphous solid

(0.730 g, 4.6 mmol, 92%), m.p. 147-149 °C. Compound has been prepared previously,[202] but NMR spectra were recorded in CD_2Cl_2.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (s, 2 H, H3), 3.99 (s, 3 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 167.0 (C2), 136.3 (C4), 117.9 (C3), 115.7 (C5), 56.9 (C1).
FTIR (ν_{max}, cm^{-1}): 3087 (w), 3074 (w), 2243 (w, C≡N), 1589 (s), 1558 (m), 1474 (m), 1437 (m), 1338 (s), 1275 (w), 1211 (w), 1194 (m), 1172 (w), 1155 (s), 1046 (s), 984 (s), 943 (w), 916 (m), 891 (s).
HRMS (ESI): calculated for $C_8H_6N_3O$ $[M+H]^+$ 160.0505, found 160.0502.
***R*$_f$** = 0.43 (40% EtOAc/hexane).



165

(4*S*,4'*S*)-2,2'-(4-Methoxypyridine-2,6-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (165): Following the general procedure for PyBOX synthesis, using 4-methoxypyridine-2,6-dicarbonitrile (**173**) (0.159 g, 1.0 mmol, 1 equiv.) and L-valinol (**167**) (0.206 g, 2.0 mmol, 2 equiv.), purified by silica gel column chromatography (eluent: 3% MeOH/CH_2Cl_2) provided the title compound as a white amorphous solid (0.216 g, 0.65 mmol, 65%), m.p. 60-62 °C (lit. m.p.[203] 83-84 °C, on material with 0.5 mol H_2O). Data are consistent with a reported example.[203]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (s, 2 H, H3), 4.50 (dd, *J* = 9.8, 8.5 Hz, 2 H, H6a), 4.20 (t, *J* = 8.5 Hz, 2 H, H6b), 4.11 (ddd, *J* = 9.8, 8.5, 6.7 Hz, 2 H, H7), 3.93 (s, 3 H, H1), 1.85 (oct, *J* = 6.7 Hz, 2 H, H8), 1.02 (d, *J* = 6.7 Hz, 6 H, H9/H10), 0.91 (d, *J* = 6.7 Hz, 6 H, H9/H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 166.6 (C2), 162.4 (C5), 148.4 (C4), 111.8 (C3), 72.9 (C7), 71.0 (C6), 56.0 (C1), 32.9 (C8), 19.2 (C9/C10), 18.3 (C9/C10).
FTIR (ν_{max}, cm^{-1}): 2964 (w), 2876 (w), 1673 (w), 1584 (m), 1533 (w), 1471 (w), 1443 (w), 1380 (w), 1346 (w), 1296 (w), 1245 (m), 1214 (m), 1182 (w), 1162 (m), 1143 (w), 1106 (w), 1082 (w), 1045 (m), 970 (s), 939 (w), 886 (w), 864 (m), 806 (w), 758 (m).

HRMS (ESI): calculated for $C_{18}H_{26}N_3O_3$ $[M+H]^+$ 332.1969, found 332.1967.

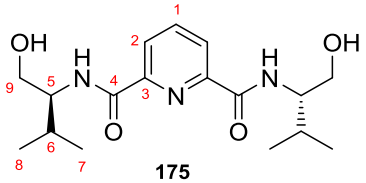
$\boldsymbol{R_f}$ = 0.28 (3% MeOH/CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28.3}}$ = -99.9 ($CHCl_3$, *c* = 1.0); lit.[203] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}$ = -83.6 (CH_2Cl_2, *c* = 0.53).

5.3.2. Synthetic procedures and characterisation for PyBIM ligands

General procedure for PyBIM synthesis: To a mixture of the appropriate amide precursor (5.0 mmol, 1 equiv.) in anhydrous $CHCl_3$ (35 mL) was added thionyl chloride (2.1 mL, 28.8 mmol, 5.8 equiv.) at 0 °C. The mixture was then heated under reflux for 5 h. Phosphorus pentachloride (2.19 g, 10.5 mmol, 2.1 equiv.) was then added in one portion and the mixture stirred under reflux for 16 h. The solution was then stripped of volatiles and the residue redissolved in anhydrous $CHCl_3$ (35 mL) to use as a stock solution of the imidoyl chloride intermediate.

To a 5 mL microwave vial was added a solution of the imidoyl chloride in $CHCl_3$ (3.5 mL, 0.5 mmol, 1 equiv.), triethylamine (0.52 mL, 3.6 mmol, 7.2 equiv.) and the appropriate aniline/amine (1.1 mmol, 2.2 equiv.). The vial was sealed and stirred at r.t. or 60 °C for the allotted time. The mixture was diluted with CH_2Cl_2 (10 mL) then quenched with 1 M aqueous NaOH solution (10 mL). The organic layer was separated and the aqueous layer extracted further with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was then purified by silica gel column chromatography.



175

***N*^{2},*N*^{6}-Bis((*S*)-1-hydroxy-3-methylbutan-2-yl)pyridine-2,6-dicarboxamide (175):** To a stirred solution of L-valinol (**167**) (2.06 g, 20.0 mmol, 2 equiv.) and triethylamine (2.79 mL, 20.0 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (50 mL) was added portionwise pyridine-2,6-dicarbonyl chloride (**174**) (2.04 g, 10.0 mmol, 1 equiv.) at 0 °C. The mixture was warmed to r.t. and stirred further for 16 h. Water (50 mL) was added and the organic layer separated. The aqueous layer was extracted further with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from CH_2Cl_2 to provide the title compound as a white crystalline solid (2.20 g, 6.5 mmol, 65%), m.p. 120-121 °C (lit. m.p.[204] 118-120 °C). Data are consistent with a reported example.[205]

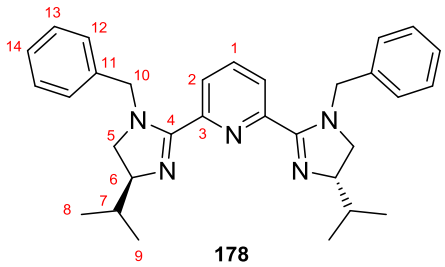
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, *J* = 7.8 Hz, 2 H, H2), 8.06 (t, *J* = 7.8 Hz, 1 H, H1), 8.00 (br d, *J* = 8.1 Hz, 2 H, NH), 3.99 – 3.93 (m, 2 H, H5), 3.89 – 3.81 (m, 4 H, H9), 2.53 (br s, 2 H, OH), 2.09 (oct, *J* = 6.8 Hz, 2 H, H6), 1.06 (d, *J* = 6.8 Hz, 6 H, H7/H8), 1.04 (d, *J* = 6.8 Hz, 6 H, H7/H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 164.2 (C4), 148.8 (C3), 139.4 (C1), 125.3 (C2), 64.2 (C9), 57.4 (C5), 29.5 (C6), 19.8 (C7/C8), 18.7 (C7/C8).

FTIR (ν_{max}, cm^{-1}): 3401 (w, NH), 3304 (br m, OH), 2964 (w), 2878 (w), 1680 (m), 1644 (s, C=O), 1592 (w), 1538 (s), 1477 (m), 1442 (w), 1389 (w), 1368 (w), 1341 (w), 1302 (w), 1238 (w), 1171 (w), 1145 (w), 1094 (w), 1066 (s), 1017 (s), 1000 (w), 970 (w), 956 (w), 934 (w), 899 (w), 872 (w), 844 (m), 800 (w).

HRMS (ESI): calculated for $C_{17}H_{27}N_3O_4Na$ $[M+Na]^+$ 360.1894, found 360.1892.

$[\alpha]_D^{25.9}$ = -37.5 ($CHCl_3$, *c* = 1.0); lit.[206] $[\alpha]_D^{25}$ = -82.3 (acetone, *c* = 0.15).



178

2,6-Bis((*S*)-1-benzyl-4-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (178): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3-methylbutan-2-yl)pyridine-2,6-dicarboxamide (**175**) and benzylamine (0.12 mL, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) provided the title compound as a brown foam (113.1 mg, 0.236 mmol, 47%). Compound has been prepared previously,[132] but NMR spectra were recorded in CD_3OD.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.9 Hz, 2 H, H2), 7.95 (t, *J* = 7.9 Hz, 1 H, H1), 7.28 – 7.23 (m, 6 H, H13 and H14), 7.14 – 7.09 (m, 4 H, H12), 4.57 (AB q, *J* = 15.3 Hz, 4 H, H10a and H10b), 3.96 (ddd, *J* = 10.7, 9.6, 6.7 Hz, 2 H, H6), 3.49 (dd, *J* = 10.7, 9.6 Hz, 2 H, H5a), 3.09 (t, *J* = 9.6 Hz, 2 H, H5b), 1.86 (oct, *J* = 6.7 Hz, 2 H, H7), 0.94 (d, *J* = 6.7 Hz, 6 H, H8/H9), 0.84 (d, *J* = 6.7 Hz, 6 H, H8/H9).

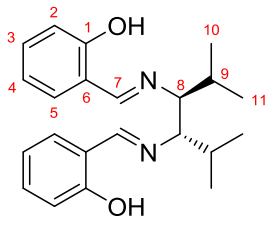
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2 (C4), 148.3 (C3), 138.3 (C1), 137.1 (C11), 128.6 (C13), 127.6 (C12), 127.5 (C14), 127.1 (C2), 68.3 (C6), 53.0 (C5), 51.7 (C10), 32.9 (C7), 18.8 (C8/C9), 17.8 (C8/C9).

FTIR (ν_{max}, cm^{-1}): 3030 (w), 2957 (m), 2871 (m), 1596 (s), 1563 (s), 1495 (m), 1454 (m), 1385 (w), 1363 (m), 1312 (w), 1263 (m), 1151 (w), 1110 (w), 1077 (w), 1029 (w), 995 (w), 925 (w), 831 (m).

HRMS (ESI): calculated for $C_{31}H_{38}N_5$ $[M+H]^+$ 480.3122, found 480.3138.

R_f = 0.07 (10% MeOH/CH_2Cl_2).

$[\alpha]_D^{27.8}$ = -130.6 ($CHCl_3$, *c* = 1.0); lit.[132] $[\alpha]_D^{25}$ = -133.5 ($CHCl_3$, *c* = 0.39).



196

2,2'-((1*E*,1'*E*)-(((3*S*,4*S*)-2,5-Dimethylhexane-3,4-diyl)bis(azanylylidene))bis(methanylylidene))diphenol (196): To a solution of (*R*,*R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (**194**) (6.92 g, 28.3 mmol, 1 equiv.) in anhydrous toluene (75 mL) was added isobutyraldehyde (**195**) (6.5 mL, 70.8 mmol, 2.5 equiv.). The mixture was heated under reflux with equipped Dean-Stark apparatus for 16 h. The mixture was then evaporated under reduced pressure and the residue triturated with MeOH. The product was collected by filtration to provide the title compound as a yellow powder (8.49 g, 24.1 mmol, 85%), m.p. 189-191 °C (lit. m.p.[133] 188-189 °C). Data are consistent with a reported example.[133]

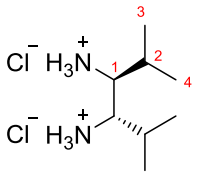
^{1}H NMR (600 MHz, $CDCl_3$): δ 13.54 (s, 2 H, OH), 8.17 (s, 2 H, H7), 7.28 – 7.24 (m, 2 H, H3), 7.15 (dd, *J* = 7.5, 1.7 Hz, 2 H, H5), 6.96 – 6.93 (m, 2 H, H2), 6.79 (td, *J* = 7.5, 1.1 Hz, 2 H, H4), 3.26 – 3.19 (m, 2 H, H8), 2.17 – 2.09 (m, 2 H, H9), 0.99 (d, *J* = 6.8 Hz, 6 H, H10/H11), 0.91 (d, *J* = 6.8 Hz, 6 H, H10/H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.8 (C7), 161.4 (C1), 132.3 (C3), 131.6 (C5), 118.57 (C4), 118.56 (C6), 117.1 (C2), 76.3 (C8), 28.6 (C9), 20.7 (C10/C11), 17.5 (C10/C11).

FTIR (ν_{max}, cm^{-1}): 2966 (w), 2927 (w), 2873 (w), 1627 (s), 1579 (m), 1499 (m), 1460 (m), 1418 (w), 1389 (w), 1364 (w), 1337 (w), 1315 (w), 1280 (m), 1207 (w), 1175 (w), 1150 (w), 1115 (w), 1083 (w), 1032 (w), 999 (w), 988 (w), 959 (w), 922 (w), 889 (w), 850 (w), 826 (w).

HRMS (ESI): calculated for $C_{22}H_{29}N_2O_2$ $[M-H]^-$ 351.2078, found 351.2077.

$[\alpha]_D^{28.4}$ = +150.0 ($CHCl_3$, *c* = 1.0); lit.[133] $[\alpha]_D^{26}$ = +144.8 ($CHCl_3$, *c* = 1.0).



197

(3*S*,4*S*)-2,5-Dimethylhexane-3,4-diammonium dichloride (197): To a solution of 2,2'-((1*E*,1'*E*)-(((3*S*,4*S*)-2,5-dimethylhexane-3,4-diyl)bis(azanylylidene))bis(methanylylidene))-diphenol (**196**) in THF (200 mL) was added 37% aqueous HCl (7.2 mL). The mixture was heated at 50 °C for 3 h, producing a white precipitate. The product was collected by filtration, providing the title compound as a white crystalline solid (4.68 g, 21.5 mmol, 89%), m.p. 284-286 °C (sublim.) (lit. m.p.[133] >200 °C (sublim.)). Data are consistent with a reported example.[133]

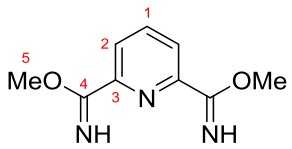
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.48 (br s, 6 H, NH), 3.21 (d, *J* = 5.4 Hz, 2 H, H1), 2.17 – 2.07 (m, 2 H, H2), 1.03 – 0.94 (m, 12 H, H3 and H4).

^{13}C NMR (150 MHz, DMSO-d_6): δ 56.2 (C1), 27.2 (C2), 19.7 (C3/C4), 17.3 (C3/C4).

FTIR (ν_{max}, cm^{-1}): 2824 (br m, NH), 1588 (s), 1555 (m), 1532 (m), 1497 (s), 1458 (m), 1379 (w), 1035 (w), 983 (w).

HRMS (ESI): calculated for $C_8H_{21}N_2$ [of free base, M+H]$^+$ 145.1699, found 145.1696.

$[\alpha]_D^{28.4}$ = -4.8 (MeOH, *c* = 1.0); lit.[133] $[\alpha]_D^{27}$ = +5.4 (MeOH, *c* = 1.0) (N.B. there appears to be a sign error in the literature optical rotation, given that their other similar (*S*,*S*)-diamine hydrochloride salts also have negative optical rotation values).



198

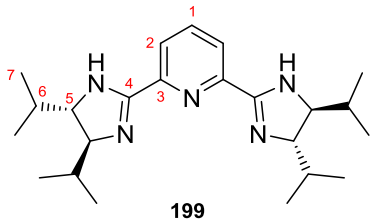
Dimethyl pyridine-2,6-bis(carbimidate) (198): To a solution of 2,6-pyridinedicarbonitrile (2.58 g, 20.0 mmol, 1 equiv.) in anhydrous MeOH (50 mL) was added sodium (60 mg, 2.5 mmol, 0.125 equiv.) and the mixture stirred at r.t. for 48 h. Acetic acid (0.15 mL, 2.5 mmol, 0.125 equiv.) was then added and the solvent removed under reduced pressure, which provided the title compound as a yellow amorphous solid (3.86 g, 20.0 mmol, 99%), m.p. >200 °C (dec.). Data are consistent with a reported example.[207]

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.23 (br s, 2 H, NH), 7.93 – 7.91 (m, 3 H, H1 and H2), 4.03 (s, 6 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.2 (C4), 147.1 (C3), 139.1 (C1), 122.7 (C2), 54.2 (C5).

FTIR (ν_{max}, cm^{-1}): 3289 (w), 3268 (m), 3008 (w), 2956 (w), 1654 (m), 1640 (m), 1571 (s), 1457 (m), 1434 (m), 1338 (s), 1268 (w), 1210 (m), 1194 (m), 1158 (w), 1080 (s), 998 (m), 946 (s), 914 (s), 874 (w), 824 (s), 751 (s).

HRMS (ESI): calculated for $C_9H_{11}N_3O_2Na$ $[M+Na]^+$ 216.0743, found 216.0749.



199

2,6-Bis((4*S*,5*S*)-4,5-diisopropyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (199): To a suspension of (3*S*,4*S*)-2,5-dimethylhexane-3,4-diammonium dichloride (**197**) (1.82 g, 8.4 mmol, 2.1 equiv.) in CH_2Cl_2 (25 mL) was added 3 M aqueous NaOH solution (20 mL). The organic layer was separated and the aqueous layer extracted further with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to provide the corresponding free base (*ca*. 1.21 g, 8.4 mmol). The free base was then dissolved in CH_2Cl_2 (20 mL) and transferred into a 20 mL microwave vial charged with dimethyl pyridine-2,6-bis(carbimidate) (**198**) (0.773 g, 4.0 mmol, 1 equiv.). The mixture was heated at 40 °C for 48 h. Water (20 mL) was then added and the organic layer separated. The aqueous layer was extracted further with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried ($MgSO_4$) then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) to provide the title compound as a white foam (0.893 g, 2.33 mmol, 58%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 7.8 Hz, 2 H, H2), 7.80 (t, *J* = 7.8 Hz, 1 H, H1), 5.90 (br s, 2 H, NH), 3.64 (br s, 4 H, H5), 1.75 (br s, 4 H, H6), 0.95 (d, *J* = 6.8 Hz, 24 H, H7).

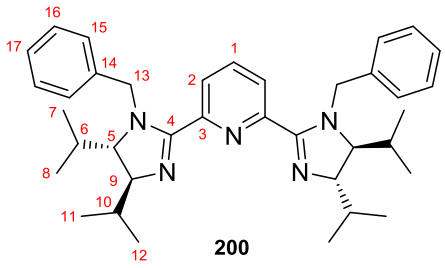
^{13}C NMR (150 MHz, $CDCl_3$): δ 160.5 (C4), 147.8 (br, C3), 137.1 (C1), 124.1 (C2), 33.4 (C6), 18.5 (C7). (C5 too broadened to distinguish properly).

FTIR (ν_{max}, cm^{-1}): 3204 (br w, NH), 2957 (m), 2871 (m), 1603 (m), 1565 (m), 1463 (s), 1385 (m), 1365 (m), 1320 (w), 1261 (m), 1240 (m), 1148 (w), 1077 (w), 992 (m), 938 (w), 832 (m).

HRMS (ESI): calculated for $C_{23}H_{38}N_5$ $[M+H]^+$ 384.3122, found 384.3130.

$\boldsymbol{R_f}$ = 0.15-0.45 (10% MeOH/CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28.3}}$ = -162.4 ($CHCl_3$, *c* = 1.0).



200

2,6-Bis((4*S*,5*S*)-1-benzyl-4,5-diisopropyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (200): To a suspension of sodium hydride (64 mg, 60% dispersion in mineral oil, 1.6 mmol, 4 equiv.) in anhydrous DMF (3 mL) was added a solution of 2,6-bis((4*S*,5*S*)-4,5-diisopropyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (**199**) (0.153 g, 0.4 mmol, 1 equiv.) in anhydrous DMF (1 mL) at 0 °C. The mixture was stirred further for 30 min. A solution of benzyl bromide (0.12 mL, 1.0 mmol, 2.5 equiv.) was added slowly dropwise over 30 min and then the mixture was warmed to r.t. and stirred for 16 h. The mixture was quenched with water (20 mL), extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts evaporated under reduced pressure. The residue was redissolved in Et_2O (25 mL), washed with water (4 × 25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) to provide the title compound as a colourless resin (0.140 g, 0.25 mmol, 62%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.8 Hz, 2 H, H2), 7.85 (t, *J* = 7.8 Hz, 1 H, H1), 7.24 – 7.17 (m, 6 H, H16 and H17), 7.12 – 7.09 (m, 4 H, H15), 5.11 (d, *J* = 15.4 Hz, 2 H, H13a), 4.24 (d, *J* = 15.4 Hz, 2 H, H13b), 3.56 (t, *J* = 5.2 Hz, 2 H, H9), 3.20 (dd, *J* = 5.2, 3.7 Hz, 2 H, H5), 1.93 – 1.84 (m, 2 H, H6), 1.53 – 1.43 (m, 2 H, H10), 0.83 (d, *J* = 6.9 Hz, 6 H, H7/H8), 0.82 (d, *J* = 6.9 Hz, 6 H, H11/H12), 0.80 (d, *J* = 6.9 Hz, 6 H, H7/H8), 0.77 (d, *J* = 6.9 Hz, 6 H, H11/H12).

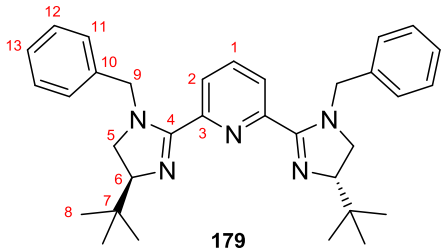
^{13}C NMR (150 MHz, $CDCl_3$): δ 161.7 (C4), 149.9 (C3), 138.0 (C14), 137.7 (C1), 128.4 (C15/C16), 128.3 (C15/C16), 127.3 (C17), 126.0 (C2), 70.5 (C9), 66.9 (C5), 49.5 (C13), 33.8 (C10), 29.6 (C6), 18.9 (C11/C12), 17.8 (C11/C12), 17.5 (C7/C8), 16.0 (C7/C8).

FTIR (ν_{max}, cm^{-1}): 2957 (m), 2870 (m), 1594 (m), 1562 (s), 1463 (s), 1399 (w), 1385 (m), 1363 (w), 1327 (w), 1261 (w), 1210 (w), 1147 (m), 1074 (m), 1025 (w), 997 (w), 966 (m), 930 (w), 833 (s).

HRMS (ESI): calculated for $C_{37}H_{50}N_5$ $[M+H]^+$ 564.4061, found 564.4071.

R_f = 0.16 (10% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.4}$ = -172.4 ($CHCl_3$, *c* = 1.0).



179

2,6-Bis((*S*)-1-benzyl-4-(*tert*-butyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (179): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and benzylamine (0.12 mL, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 10% MeOH/EtOAc) provided the title compound as a brown gum (100.1 mg, 0.197 mmol, 39%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (br d, *J* = 7.7 Hz, 2 H, H2), 7.87 (t, *J* = 7.7 Hz, 1 H, H1), 7.29 – 7.23 (m, 6 H, H12 and H13), 7.17 – 7.13 (m, 4 H, H11), 4.60 (d, *J* = 15.2 Hz, 2 H, H9a), 4.53 (br d, *J* = 15.2 Hz, 2 H, H9b), 3.84 (appears t, *J* = 10.6 Hz, 2 H, H6), 3.40 (t, *J* = 10.6 Hz, 2 H, H5a), 3.07 (appears t, *J* = 9.9 Hz, 2 H, H5b), 0.88 (s, 18 H, H8).

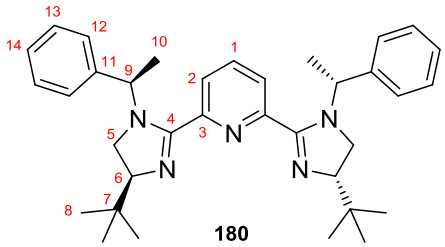
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.7 (C4), 137.9 (C1), 128.6 (C12), 127.9 (C11), 127.4 (C10), 127.3 (C11), 126.3 – 126.0 (br, C2), 73.6 – 73.1 (br, C6), 51.9 (C5/C9), 51.8 (C5/C9), 34.3 (C7), 26.2 (C8). (C3 too broadened to distinguish properly).

FTIR (ν_{max}, cm^{-1}): 3029 (w), 2952 (s), 2866 (m), 1594 (m), 1565 (s), 1495 (m), 1454 (s), 1390 (m), 1362 (s), 1275 (m), 1148 (m), 1076 (m), 1028 (m), 829 (m).

HRMS (ESI): calculated for $C_{33}H_{42}N_5$ $[M+H]^+$ 508.3435, found 508.3423.

R_f = 0.14 (15% MeOH/EtOAc).

$[\alpha]_D^{25.9}$ = -140.4 ($CHCl_3$, *c* = 1.0).



180

2,6-Bis((*S*)-4-(*tert*-butyl)-1-((*R*)-1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (180): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and (*R*)-1-phenylethan-1-amine (0.14 mL, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a brown gum (26.3 mg, 0.049 mmol, 10%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (br s, 2 H, H2), 8.05 (t, *J* = 7.7 Hz, 1 H, H1), 7.32 – 7.25 (m, 10 H, H12, H13 and H14), 5.67 (br s, 2 H, H9), 3.86 (t, *J* = 10.7 Hz, 2 H, H6), 3.29 (appears br t, *J* = 9.1 Hz, 2 H, H5a), 3.18 (appears t, *J* = 10.7 Hz, 2 H, H5b), 1.42 (d, *J* = 6.8 Hz, 6 H, H10), 0.97 (s, 18 H, H8).

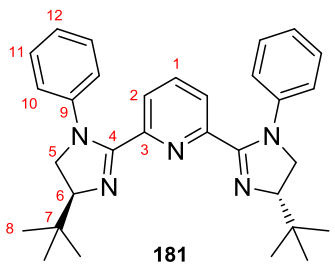
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.4 (C4), 138.9 (C1), 128.8 (C12/C13), 128.1 (br, C2), 127.8 (C14), 127.1 (C12/C13), 53.2 (C9), 46.1 (C5), 34.6 (C7), 25.9 (C8), 16.3 (C10). (C11 appears to be hidden behind other aromatic carbon peaks; C3, C6 too broadened to distinguish properly).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 2866 (w), 1592 (m), 1562 (s), 1454 (m), 1391 (w), 1362 (m), 1279 (s), 1205 (m), 1174 (m), 1078 (w), 1024 (m), 994 (w), 827 (m), 787 (m).

HRMS (ESI): calculated for $C_{35}H_{46}N_5$ $[M+H]^+$ 536.3748, found 536.3737.

R_f = 0.06 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{26.1}$ = +37.2 ($CHCl_3$, *c* = 1.0).



181

2,6-Bis((*S*)-4-(*tert*-butyl)-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (181): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-

dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and aniline (0.10 mL, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a pale brown gum (213.0 mg, 0.444 mmol, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 – 7.60 (m, 3 H, H1 and H2), 7.09 (t, *J* = 7.6 Hz, 4 H, H11), 6.92 (t, *J* = 7.6 Hz, 2 H, H12), 6.60 (d, *J* = 7.6 Hz, 4 H, H10), 4.02 (dd, *J* = 10.9, 9.3 Hz, 2 H, H5a), 3.93 (dd, *J* = 10.9, 7.6 Hz, 2 H, H6), 3.60 (dd, *J* = 9.3, 7.6 Hz, 2 H, H5b), 0.91 (s, 18 H, H8).

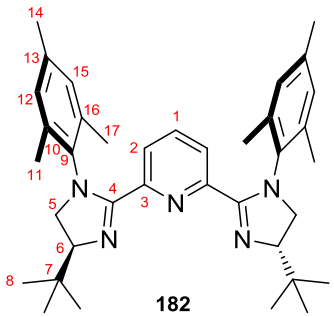
^{13}C NMR (150 MHz, $CDCl_3$): δ 159.8 (C4), 149.9 (C3), 143.1 (C9), 136.7 (C1), 128.4 (C11), 124.6 (C2), 123.3 (C12), 122.8 (C10), 74.1 (C6), 55.1 (C5), 34.3 (C7), 26.0 (C8).

FTIR (ν_{max}, cm^{-1}): 2954 (w), 2868 (w), 1595 (m), 1569 (m), 1496 (s), 1480 (s), 1425 (w), 1392 (m), 1362 (m), 1299 (w), 1280 (w), 1216 (w), 1168 (w), 1082 (w), 1049 (w), 1018 (w), 994 (w), 931 (w), 825 (w).

HRMS (ESI): calculated for $C_{31}H_{38}N_5$ $[M+H]^+$ 480.3122, found 480.3109.

R_f = 0.11 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{25.9}$ = +35.3 ($CHCl_3$, *c* = 1.0).



182

2,6-Bis((*S*)-4-(*tert*-butyl)-1-mesityl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (182): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 2,4,6-trimethylaniline (0.16 mL, 1.1 mmol, 2.2 equiv.) at r.t. for 48 h, purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) provided the title compound as a pale brown gum (68.9 mg, 0.122 mmol, 24%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (br t, *J* = 7.9 Hz, 1 H, H1), 7.51 (d, *J* = 7.9 Hz, 2 H, H2), 6.82 (s, 2 H, H12/H15), 6.71 (s, 2 H, H12/H15), 4.21 (appears t, *J* = 11.3 Hz, 2 H, H6), 3.93

(t, *J* = 11.3 Hz, 2 H, H5a), 3.57 (appears t, *J* = 10.8 Hz, 2 H, H5b), 2.24 (s, 6 H, H11/H17), 2.18 (s, 6 H, H14), 1.82 (s, 6 H, H11/H17), 1.05 (s, 18 H, H8).

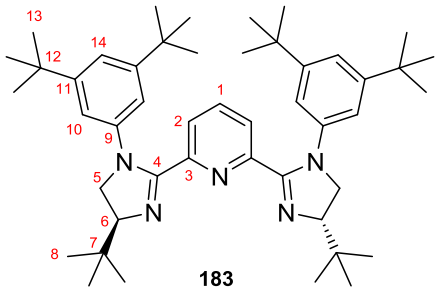
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.5 (C4), 146.0 (C3), 138.3 (C9), 137.6 (C1), 136.1 (C10/C16), 134.8 (C10/C16), 134.1 (C13), 130.0 (C12/C15), 129.9 (C12/C15), 126.4 (C2), 70.7 (C6), 53.8 (C5), 34.3 (C7), 26.2 (C8), 20.9 (C14), 18.2 (C11/C17), 17.9 (C11/C17).

FTIR (ν_{max}, cm^{-1}): 2952 (s), 2867 (m), 1612 (m), 1558 (s), 1479 (s), 1362 (w), 1280 (m), 1172 (w), 1018 (w), 853 (w), 823 (w).

HRMS (ESI): calculated for $C_{37}H_{50}N_5$ $[M+H]^+$ 564.4061, found 564.4053.

R_f = 0.11 (10% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.4}$ = +19.6 ($CHCl_3$, *c* = 1.0).



183

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(3,5-di-*tert*-butylphenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (183): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 3,5-di-*tert*-butylaniline (0.226 g, 1.1 mmol, 2.2 equiv.) at r.t. for 16 h, purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) provided the title compound as a yellow foam (201.3 mg, 0.286 mmol, 57%).

^{1}H NMR (600 MHz, MeOD-d_4): δ 7.80 (t, *J* = 8.0 Hz, 1 H, H1), 7.41 (d, *J* = 8.0 Hz, 2 H, H2), 7.36 (t, *J* = 1.5 Hz, 2 H, H14), 6.94 (d, *J* = 1.5 Hz, 4 H, H10), 4.39 (t, *J* = 10.7 Hz, 2 H, H5a), 4.21 (dd, *J* = 10.7, 8.1 Hz, 2 H, H6), 4.16 (dd, *J* = 10.7, 8.1 Hz, 2 H, H5b), 1.24 (s, 36 H, H13), 1.06 (s, 18 H, H8).

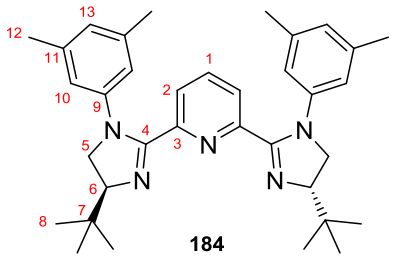
^{13}C NMR (150 MHz, MeOD-d_4): δ 162.2 (C4), 153.9 (C9), 147.3 (C3), 140.2 (C11), 139.1 (C1), 128.4 (C2), 122.3 (C14), 120.0 (C10), 70.9 (C6), 57.4 (C5), 35.9 (C12), 35.3 (C7), 31.7 (C13), 25.8 (C8).

FTIR (ν_{max}, cm^{-1}): 2954 (s), 2868 (m), 1594 (s), 1567 (m), 1479 (m), 1393 (w), 1362 (m), 1334 (w), 1248 (m), 1203 (w), 1168 (w), 1084 (w), 993 (w), 900 (w), 864 (w), 827 (w), 751 (m).

HRMS (ESI): calculated for $C_{47}H_{70}N_5$ $[M+H]^+$ 704.5626, found 704.5618.

$\boldsymbol{R_f}$ = 0.14 (10% MeOH/CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28.4}}$ = -70.6 ($CHCl_3$, *c* = 1.0).



184

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(3,5-dimethylphenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (184): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 3,5-dimethylaniline (0.16 mL, 1.1 mmol, 2.2 equiv.) at r.t. for 16 h, purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) provided the title compound as an orange resin (206.3 mg, 0.385 mmol, 77%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (br d, *J* = 7.7 Hz, 2 H, H2), 7.77 (br t, *J* = 7.7 Hz, 1 H, H1), 6.71 (s, 2 H, H13), 6.34 (s, 4 H, H10), 4.12 (t, *J* = 10.5 Hz, 2 H, H5a), 4.04 (dd, *J* = 10.5, 7.9 Hz, 2 H, H6), 3.76 (dd, *J* = 10.5, 7.9 Hz, 2 H, H5b), 2.16 (s, 12 H, H12), 0.94 (s, 18 H, H8).

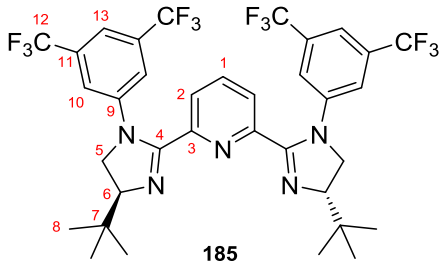
^{13}C NMR (150 MHz, $CDCl_3$): δ 160.0 (C4), 146.2 – 145.8 (br, C3), 140.3 – 140.1 (C9), 138.7 (C11), 137.8 – 137.7 (br, C1), 127.7 – 127.5 (br, C2/C13), 127.5 – 127.3 (br, C2/C13), 121.3 (C10), 70.4 – 70.0 (br, C6), 55.7 (C5), 34.4 (C7), 25.6 (C8), 21.3 (C12).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 1595 (s), 1567 (s), 1476 (s), 1363 (w), 1337 (w), 1275 (w), 1217 (w), 994 (w), 834 (w).

HRMS (ESI): calculated for $C_{35}H_{46}N_5$ $[M+H]^+$ 536.3748, found 536.3735.

$\boldsymbol{R_f}$ = 0.05 (10% MeOH/CH_2Cl_2).

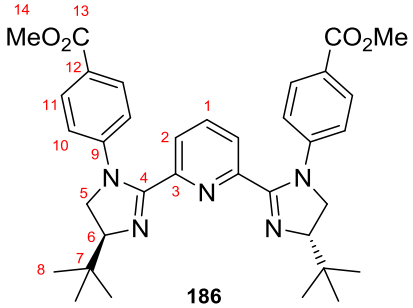
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28.4}}$ = -18.6 ($CHCl_3$, *c* = 1.0).



185

2,6-Bis((*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-4-(*tert*-butyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (185): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 3,5-bis(trifluoromethyl)aniline (0.10 mL, 0.66 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 3% MeOH/CH_2Cl_2) provided the title compound as a light brown foam (163.0 mg, 0.212 mmol, 43%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.8 Hz, 2 H, H2), 7.85 (t, *J* = 7.8 Hz, 1 H, H1), 7.37 (s, 2 H, H13), 6.88 (q, *J* = 1.1 Hz, 4 H, H10), 3.98 (dd, *J* = 10.6, 7.4 Hz, 2 H, H6), 3.92 (dd, *J* = 10.6, 8.9 Hz, 2 H, H5a), 3.65 (dd, *J* = 8.9, 7.4 Hz, 2 H, H5b), 0.90 (s, 18 H, H8).
^{13}C NMR (150 MHz, $CDCl_3$): δ 157.3 (C4), 148.3 – 148.2 (br, C3), 143.9 (C9), 137.8 (C1), 131.5 (q, *J* = 33.3 Hz, C11), 125.6 (C2), 123.1 (q, *J* = 272.8 Hz, C12), 121.1 – 120.09 (br, C10), 115.8 – 115.5 (br, C13), 74.2 (C6), 54.5 (C5), 34.4 (C7), 25.8 (C8).
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.2 (s, 12 F, F12).
FTIR (ν_{max}, cm^{-1}): 2960 (w), 2871 (w), 1685 (w), 1610 (w), 1570 (w), 1520 (w), 1475 (m), 1396 (m), 1365 (m), 1274 (s), 1171 (m), 1126 (s), 1108 (m), 1057 (m), 1022 (w), 996 (w), 879 (w), 846 (w), 827 (w), 756 (m).
HRMS (ESI): calculated for $C_{35}H_{34}F_{12}N_5$ $[M+H]^+$ 752.2617, found 752.2640.
R_f = 0.29 (4% MeOH/CH_2Cl_2).
$[\alpha]_D^{28.4}$ = -100.1 ($CHCl_3$, *c* = 1.0).



Dimethyl 4,4'-((4*S*,4'*S*)-pyridine-2,6-diylbis(4-(*tert*-butyl)-4,5-dihydro-1*H*-imidazole-2,1-diyl))dibenzoate (186): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and methyl 4-aminobenzoate (0.166 g, 1.1 mmol, 2.2 equiv.) at r.t. for 72 h, purified by silica gel column chromatography (eluent: 4% → 10% MeOH/CH_2Cl_2) provided the title compound as an orange foam (132.0 mg, 0.222 mmol, 44%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 – 7.75 (m, 3 H, H1 and H2), 7.73 (d, *J* = 8.8 Hz, 4 H, H11), 6.50 (d, *J* = 8.8 Hz, 4 H, H10), 3.98 – 3.91 (m, 4 H, H5a and H6), 3.85 (s, 6 H, H14), 3.71 – 3.63 (m, 2 H, H5b), 0.89 (s, 18 H, H8).

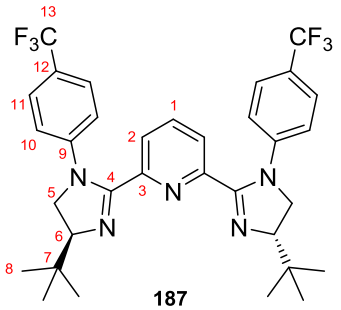
^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8 (C13), 158.4 (C4), 149.7 (br, C3), 146.5 (C9), 137.5 (C1), 130.1 (C11), 125.0 (C2), 123.7 (C12), 120.5 (C10), 74.1 (C6), 54.2 (C5), 52.0 (C14), 34.3 (C7), 25.9 (C8).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 2869 (w), 1715 (s, C=O), 1603 (s), 1568 (m), 1516 (m), 1479 (m), 1434 (m), 1382 (m), 1363 (m), 1332 (w), 1276 (s), 1181 (m), 1112 (m), 1048 (w), 1000 (w), 932 (w), 847 (w), 827 (w), 769 (m), 753 (m).

HRMS (ESI): calculated for $C_{35}H_{42}N_5O_4$ $[M+H]^+$ 596.3231, found 596.3228.

R_f = 0.26 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{25.1}$ = -47.1 ($CHCl_3$, *c* = 1.0).



187

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (187): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 4-trifluoromethylaniline (0.14 mL, 1.1 mmol, 2.2 equiv.) at r.t. for 16 h, purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a yellow gum (215.1 mg, 0.349 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.8 Hz, 2 H, H2), 7.79 (t, *J* = 7.8 Hz, 1 H, H1), 7.27 (d, *J* = 8.5 Hz, 4 H, H11), 6.51 (d, *J* = 8.5 Hz, 4 H, H10), 3.96 – 3.88 (m, 4 H, H5a and H6), 3.66 – 3.59 (m, 2 H, H5b), 0.90 (s, 18 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.1 (C4), 149.1 (C3), 145.4 (C9), 137.5 (C1), 125.3 (q, *J* = 3.7 Hz, C11), 125.1 (C2), 124.4 (q, *J* = 271.3 Hz, C13), 124.1 (q, *J* = 32.6 Hz, C12), 121.2 (C10), 73.9 (C6), 54.3 (C5), 34.3 (C7), 25.8 (C8).

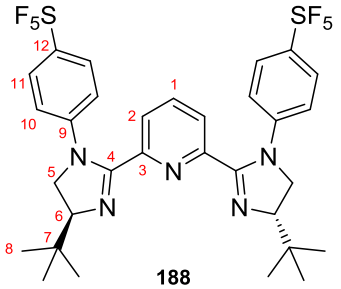
^{19}F NMR (376 MHz, $CDCl_3$): δ -61.8 (s, 6 F, F13).

FTIR (ν_{max}, cm^{-1}): 2953 (w), 1604 (w), 1569 (w), 1523 (w), 1481 (w), 1412 (w), 1364 (w), 1323 (s), 1161 (m), 1114 (m), 1070 (m), 1047 (w), 1014 (w), 833 (w), 757 (w).

HRMS (ESI): calculated for $C_{33}H_{36}F_6N_5$ $[M+H]^+$ 616.2869, found 616.2861.

R_f = 0.07 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.4}$ = -44.5 ($CHCl_3$, *c* = 1.0).

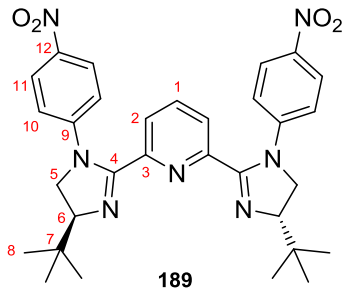


188

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(4-(pentafluorosulfanyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (188): Following the general procedure for PyBIM synthesis, using N^2,N^6-

bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 4-(pentafluorothio)aniline (**207**) (0.241 g, 1.1 mmol, 2.2 equiv.) at r.t. for 72 h, purified by silica gel column chromatography (eluent: 3% → 5% MeOH/CH_2Cl_2) provided the title compound as an off-white foam (208.6 mg, 0.285 mmol, 57%). For scale-up to 5.0 mmol with respect to the imidoyl chloride, the general procedure was slightly modified, using 4-(pentafluorothio)aniline (**207**) (3.29 g, 15.0 mmol, 3 equiv.), which provided the title compound as an off-white foam (1.54 g, 2.1 mmol, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.8 Hz, 2 H, H2), 7.83 (t, *J* = 7.8 Hz, 1 H, H1), 7.36 (d, *J* = 9.0 Hz, 4 H, H11), 6.41 (d, *J* = 9.0 Hz, 4 H, H10), 3.95 – 3.87 (m, 4 H, H5a and H6), 3.66 – 3.58 (m, 2 H, H5b), 0.91 (s, 18 H, H8).
^{13}C NMR (150 MHz, $CDCl_3$): δ 157.4 (C4), 148.5 (C3), 147.5 (qn, *J* = 17.3 Hz, C12), 144.7 (C9), 137.6 (C1), 125.7 (qn, *J* = 4.1 Hz, C11), 125.4 (C2), 120.4 (C10), 73.7 (C6), 54.2 (C5), 34.3 (C7), 25.8 (C8).
^{19}F NMR (376 MHz, $CDCl_3$): δ 86.3 (qn, *J* = 150.1 Hz, 2 F, SF_{ax}), 63.9 (d, *J* = 150.1 Hz, 8 F, SF_{eq}).
FTIR (ν_{max}, cm^{-1}): 2958 (w), 1596 (m), 1570 (w), 1507 (m), 1481 (m), 1429 (w), 1393 (m), 1365 (w), 1334 (w), 1208 (w), 1160 (w), 1103 (m), 1012 (w), 828 (s, S-F), 757 (w).
HRMS (ESI): calculated for $C_{31}H_{36}F_{10}N_5S_2$ $[M+H]^+$ 732.2247, found 732.2236.
R_f = 0.09 (5% MeOH/CH_2Cl_2).
$[\alpha]_D^{25.1}$ = -63.4 ($CHCl_3$, *c* = 1.0).



189

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (189): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 4-nitroaniline (0.152 g, 1.1 mmol, 2.2 equiv.) at r.t. for 72 h, purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a yellow foam (119.7 mg, 0.210 mmol, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.7 Hz, 2 H, H2), 7.91 – 7.85 (m, 5 H, H1 and H10), 6.46 (d, *J* = 9.0 Hz, 4 H, H11), 4.00 – 3.94 (m, 2 H, H6), 3.90 (appears t, *J* = 9.8 Hz, 2 H, H5a), 3.69 (appears t, *J* = 8.4 Hz, 2 H, H5b), 0.89 (s, 18 H, H8).

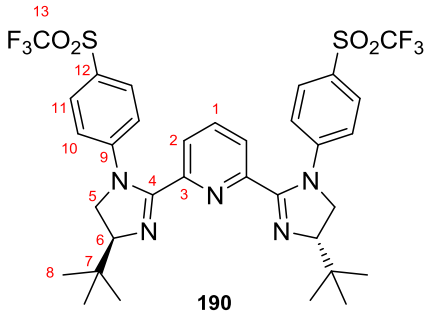
^{13}C NMR (150 MHz, $CDCl_3$): δ 157.2 (C4), 149.1 (C3), 147.5 (C12), 141.7 (C9), 138.1 (C1), 125.4 (C2), 124.2 (C11), 119.8 (C10), 74.1 (C6), 53.9, (C5) 34.2 (C7), 25.8 (C8).

FTIR (ν_{max}, cm^{-1}): 2956 (w), 1590 (m), 1504 (m, NO_2), 1478 (w), 1431 (w), 1389 (w), 1364 (w), 1325 (s, NO_2), 1249 (w), 1187 (w), 1154 (w), 1113 (m), 1048 (w), 1000 (w), 854 (w), 843 (w), 751 (m).

HRMS (ESI): calculated for $C_{31}H_{36}N_7O_4$ $[M+H]^+$ 570.2823, found 570.2819.

R_f = 0.08 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{25.1}$ = -95.1 ($CHCl_3$, *c* = 1.0).



190

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(4-((trifluoromethyl)sulfonyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (190): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 4-((trifluoromethyl)sulfonyl)aniline (0.248 g, 1.1 mmol, 2.2 equiv.) at r.t. for 72 h, purified by silica gel column chromatography (eluent: 3% → 5% MeOH/CH_2Cl_2) provided the title compound as a yellow gum (69.6 mg, 0.094 mmol, 19%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.8 Hz, 2 H, H2), 7.94 (t, *J* = 7.8 Hz, 1 H, H1), 7.61 (d, *J* = 8.8 Hz, 4 H, H11), 6.53 (d, *J* = 8.8 Hz, 4 H, H10), 3.99 (dd, *J* = 9.8, 7.7 Hz, 2 H, H6), 3.91 (t, *J* = 9.8 Hz, 2 H, H5a), 3.71 (dd, *J* = 9.8, 7.7 Hz, 2 H, H5b), 0.94 (s, 18 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.5 (C4), 148.8 (C9), 148.3 (C3), 138.2 (C1), 131.0 (C11), 125.8 (C2), 121.8 (C12), 120.3 (C10), 120.1 (q, *J* = 325.7 Hz, C13), 74.0 (C6), 53.9 (C5), 34.3 (C7), 25.9 (C8).

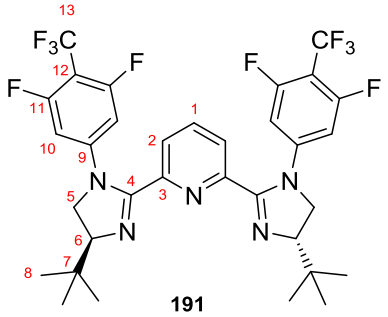
^{19}F NMR (376 MHz, $CDCl_3$): δ -78.6 (s, 6 F, F13).

FTIR (ν_{max}, cm^{-1}): 2958 (m), 1587 (s), 1502 (m), 1479 (m), 1412 (w), 1216 (s), 1193 (s), 1141 (s), 1076 (s), 1003 (w), 830 (m), 768 (m).

HRMS (ESI): calculated for $C_{33}H_{36}F_6N_5O_4S_2$ $[M+H]^+$ 744.2107, found 744.2117.

R_f = 0.31 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{25.4}$ = -85.0 ($CHCl_3$, *c* = 1.0).



191

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (191): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**176**) and 3,5-difluoro-4-(trifluoromethyl)aniline (0.217 g, 1.1 mmol, 2.2 equiv.) at r.t. for 72 h, purified by silica gel column chromatography (eluent: 3% MeOH/CH_2Cl_2) provided the title compound as a white foam (31.0 mg, 0.045 mmol, 9%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.8 Hz, 2 H, H2), 7.91 (t, *J* = 7.8 Hz, 1 H, H1), 6.05 (d, *J* = 11.3 Hz, 4 H, H10), 3.99 (dd, *J* = 10.0, 8.2 Hz, 2 H, H6), 3.86 (t, *J* = 10.0 Hz, 2 H, H5a), 3.69 (dd, *J* = 10.0, 8.2 Hz, 2 H, H5b), 0.93 (s, 18 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.7 (approx. dd, *J* = 256.0, 7.5 Hz, C11), 156.6 (C4), 148.2 (C3), 146.9 (t, *J* = 14.1 Hz, C9), 138.1 (C1), 125.8 (C2), 122.0 (q, *J* = 272.3 Hz, C13), 104.3 (d, *J* = 28.5 Hz, C10), 101.0-100.0 (br, C12), 74.0 (C6), 54.0 (C5), 34.3 (C7), 25.8 (C8).

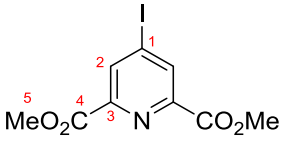
^{19}F NMR (376 MHz, $CDCl_3$): δ -55.5 (t, *J* = 21.3 Hz, 6 F, F13), -111.5 (q, *J* = 21.3 Hz, 4 F, F11).

FTIR (ν_{max}, cm^{-1}): 2958 (w), 2873 (w), 1644 (m), 1606 (m), 1576 (m), 1514 (w), 1480 (w), 1415 (w), 1400 (w), 1365 (w), 1301 (s), 1226 (m), 1186 (w), 1130 (m), 1083 (w), 1046 (m), 1033 (w), 1006 (w), 834 (w), 756 (w).

HRMS (ESI): calculated for $C_{33}H_{32}F_{10}N_5$ $[M+H]^+$ 688.2493, found 688.2493.

R_f = 0.29 (3% MeOH/CH_2Cl_2).

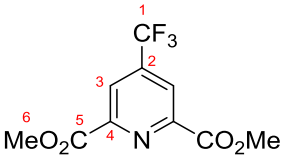
$[\alpha]_D^{25.0}$ = -53.6 ($CHCl_3$, *c* = 0.5).



202

Dimethyl 4-iodopyridine-2,6-dicarboxylate (202): To a solution of dimethyl 4-chloro-2,6,dicarboxylate (**201**) (4.66 g, 20.3 mmol, 1 equiv.) in anhydrous MeCN (150 mL) was added acetyl chloride (4.33 mL, 60.9 mmol, 3 equiv.) and then sodium iodide (60.9 g, 406.0 mmol, 20 equiv.). The mixture was sonicated for 5 h, keeping the bath temperature below 30 °C. The mixture was then cooled to 0 °C and saturated aqueous Na_2CO_3 solution (75 mL) and CH_2Cl_2 (150 mL) were added. The organic layer was separated and then washed with saturated aqueous $Na_2S_2O_3$ solution (100 mL), water (2 × 100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from MeOH to provide the title compound as white crystalline needles (4.35 g, 13.6 mmol, 67%), m.p. 175-176 °C (lit. m.p.[208] 174-175 °C). Data are consistent with a reported example.[208]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.66 (s, 2 H, H2), 4.02 (s, 6 H, H5).
^{13}C NMR (150 MHz, $CDCl_3$): δ 164.0 (C4), 148.4 (C3), 137.3 (C2), 107.1 (C1), 53.6 (C5).
FTIR (ν_{max}, cm^{-1}): 3068 (w), 2949 (w), 1708 (s, C=O), 1566 (m), 1442 (s), 1324 (s), 1262 (s), 1241 (m), 1194 (m), 1142 (s), 981 (m), 960 (m), 888 (m), 825 (m), 778 (s).
HRMS (ESI): calculated for $C_9H_9NO_4I$ $[M+H]^+$ 321.9571, found 321.9578.

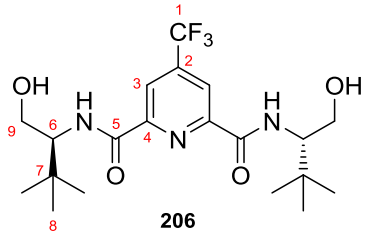


204

Dimethyl 4-(trifluoromethyl)pyridine-2,6-dicarboxylate (204): To a mixture of dimethyl 4-iodopyridine-2,6-dicarboxylate (**202**) (1.41 g, 4.4 mmol, 1 equiv.), copper(I) iodide (4.99 g, 26.2 mmol, 6 equiv.) and (dppf)$PdCl_2$•CH_2Cl_2 (0.18 g, 0.22 mmol, 0.05 equiv.) in anhydrous DMF (70 mL) was added a solution of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**203**) (5.03 g, 26.2 mmol, 6 equiv.) in anhydrous DMF (20 mL). The mixture was stirred at 100 °C for 16 h. The mixture was cooled to r.t. then diluted with CH_2Cl_2 (150 mL). The mixture was filtered through a pad of Celite, eluting with CH_2Cl_2, then the filtrate was washed with water (2 × 250 mL), brine/water (1:1, 250 mL), brine (250 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography

(eluent: 40% EtOAc/hexane) to provide the title compound as a yellow amorphous solid (1.03 g, 3.93 mmol, 89%), m.p. 122-123 °C (lit. m.p.[134] 122-124 °C). Data are consistent with a reported example.[134]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (s, 2 H, H3), 4.07 (s, 6 H, H6).
^{13}C NMR (150 MHz, $CDCl_3$): δ 164.1 (C5), 149.8 (C4), 141.3 (q, *J* = 35.6 Hz, C2), 123.9 (q, *J* = 3.5 Hz, C3), 122.1 (q, *J* = 273.8 Hz, C1), 53.8 (C6).
^{19}F NMR (376 MHz, $CDCl_3$): δ -64.7 (s, 3 F, F1).
FTIR (ν_{max}, cm^{-1}): 3083 (w), 2964 (w), 1718 (s, C=O), 1630 (w), 1448 (m), 1435 (w), 1383 (w), 1274 (s), 1252 (s), 1198 (m), 1168 (s), 1129 (s), 985 (m), 970 (m), 936 (m), 891 (m), 851 (m), 784 (m).
HRMS (ESI): calculated for $C_{10}H_9F_3NO_4$ $[M+H]^+$ 264.0478, found 264.0482.
R_f = 0.51 (40% EtOAc/hexane).



206

***N*^{2},*N*^{6}-Bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl)pyridine-2,6-dicarboxamide (206):** To a 5 mL microwave vial was added dimethyl 4-(trifluoromethyl)pyridine-2,6-dicarboxylate (**204**) (0.526 g, 2.0 mmol, 1 equiv.) and L-*tert*-leucinol (**205**) (0.516 g, 4.4 mmol, 2.2 equiv.). The neat mixture was stirred at 120 °C for 2.5 h, whereupon a precipitate formed. The residue was purified by silica gel column chromatography (60% EtOAc/hexane → EtOAc) to provide the title compound as a white amorphous solid (0.837 g, 1.93 mmol, 96%), m.p. 186-188 °C (lit. m.p.[134] 178-180 °C). Compound has been prepared previously,[134] but NMR spectra were recorded in DMSO-d_6.

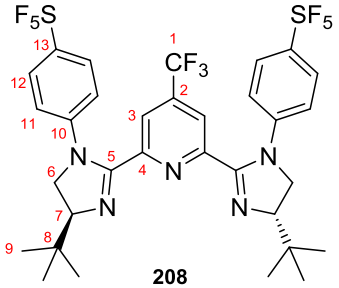
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (s, 2 H, H3), 8.04 (br d, *J* = 9.1 Hz, 2 H, NH), 4.05 – 3.99 (m, 2 H, H6), 3.99 – 3.94 (m, 2 H, H9a), 3.82 – 3.75 (m, 2 H, H9b), 2.23 (br s, 2 H, OH), 1.06 (s, 18 H, H8).
^{13}C NMR (150 MHz, $CDCl_3$): δ 163.0 (C5), 150.4 (C4), 142.2 (q, *J* = 35.3 Hz, C2), 122.3 (q, *J* = 274.0 Hz, C1), 121.4 (q, *J* = 3.4 Hz, C3), 63.2 (C9), 59.9 (C6), 34.2 (C7), 27.2 (C8).
^{19}F NMR (376 MHz, $CDCl_3$): δ -64.8 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 3390 (br w, OH), 3324 (w, NH), 2967 (w), 1741 (w), 1664 (s, C=O), 1609 (w), 1539 (s), 1478 (w), 1435 (w), 1412 (w), 1366 (w), 1334 (w), 1283 (m), 1239 (w), 1220 (w), 1178 (m), 1151 (m), 1140 (s), 1096 (m), 1058 (w), 1046 (m), 1023 (w), 999 (w), 933 (w), 903 (w), 797 (w), 778 (w).

HRMS (ESI): calculated for $C_{20}H_{29}F_3N_3O_4$ $[M-H]^-$ 432.2116, found 432.2114.

R_f = 0.20 (50% EtOAc/hexane).

$[\alpha]_D^{28.4}$ = -5.2 ($CHCl_3$, *c* = 0.25); lit.[134] $[\alpha]_D^{28}$ = +6.32 (MeOH, *c* = 0.27).



208

2,6-Bis((*S*)-4-(*tert*-butyl)-1-(4-(pentafluorosulfanyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)-4-(trifluoromethyl)pyridine (208): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl)-pyridine-2,6-dicarboxamide (**206**) and 4-(pentafluorothio)aniline (**207**) (0.241 g, 1.1 mmol, 2.2 equiv.) at 60 °C for 5 d, purified by silica gel column chromatography (eluent: 1% → 1.5% MeOH/CH_2Cl_2) provided the title compound as an off-white amorphous solid (196.0 mg, 0.245 mmol, 49%), m.p. 201-202 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (s, 2 H, H3), 7.38 (d, *J* = 8.9 Hz, 4 H, H12), 6.36 (d, *J* = 8.9 Hz, 4 H, H11), 3.95 (dd, *J* = 10.7, 7.7 Hz, 2 H, H7), 3.88 (dd, *J* = 10.7, 9.2 Hz, 2 H, H6a), 3.64 (dd, *J* = 9.2, 7.7 Hz, 2 H, H6b), 0.94 (s, 18 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.4 (C5), 149.5 (C4), 147.9 (qn, *J* = 17.1 Hz, C13), 144.5 (C10), 140.1 (q, *J* = 34.8 Hz, C2), 125.8 (qn, *J* = 4.2 Hz, C12), 122.4 (q, *J* = 273.9 Hz, C1), 121.3 (q, *J* = 3.5 Hz, C3), 120.8 (C11), 73.9 (C7), 54.5 (C6), 34.4 (C8), 25.9 (C9).

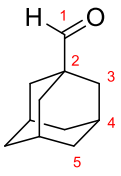
^{19}F NMR (376 MHz, $CDCl_3$): δ 86.1 (qn, *J* = 150.1 Hz, 2 F, SF_{ax}), 63.9 (d, *J* = 150.1 Hz, 8 F, SF_{eq}), -64.5 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 2959 (w), 2871 (w), 1594 (m), 1571 (m), 1506 (m), 1481 (m), 1448 (w), 1412 (w), 1395 (w), 1364 (m), 1327 (m), 1288 (m), 1269 (m), 1179 (m), 1147 (m), 1103 (m), 1024 (w), 907 (w), 826 (s, S-F), 790 (m), 755 (m).

HRMS (ESI): calculated for $C_{32}H_{35}N_5F_{13}S_2$ $[M+H]^+$ 800.2121, found 800.2103.

R_f = 0.20 (1% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.4}$ = -84.2 ($CHCl_3$, *c* = 1.0).



210

1-Adamantanecarboxaldehyde (210): To a solution of anhydrous DMSO (3.55 mL, 50.0 mmol, 2.5 equiv.) in anhydrous CH_2Cl_2 (50 mL) at -78 °C was added oxalyl chloride (2.20 mL, 26.0 mmol, 1.3 equiv.) slowly dropwise, keeping the internal temperature below -60 °C. The mixture was stirred further for 15 min. A solution of 1-adamantanemethanol (**209**) (3.35 g, 20.0 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (25 mL) was added slowly dropwise and the mixture then stirred for 1 h. Triethylamine (13.9 mL, 100.0 mmol, 5 equiv.) was then added and stirred for 30 min. The mixture was warmed to r.t., quenched with 10% aqueous KH_2PO_4 (50 mL) and diluted with Et_2O (50 mL). The organic layer was separated, washed with 10% aqueous KH_2PO_4 (3 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: CH_2Cl_2) to provide the title compound as a white amorphous solid (3.07 g, 18.7 mmol, 94%), m.p. 147-148 °C (lit. m.p.[209] 146-148 °C). Data are consistent with a reported example.[209]

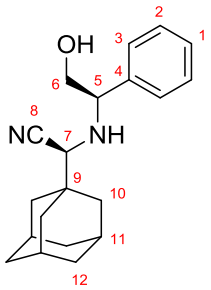
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.28 (s, 1 H, H1), 2.04 (s, 3 H, H4), 1.74 (d, *J* = 12.3 Hz, 3 H, H5a), 1.69 (s, 6 H, H3), 1.66 (d, *J* = 12.3 Hz, 3 H, H5b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.1 (C1), 44.9 (C2), 36.6 (C5), 35.8 (C3), 27.4 (C4).

FTIR (ν_{max}, cm^{-1}): 2904 (s), 2850 (m), 2696 (w), 1802 (w), 1721 (s, C=O), 1451 (m), 1344 (w), 1264 (w), 1193 (w), 1143 (w), 1105 (w), 1052 (w), 988 (w), 905 (m).

HRMS (ESI): calculated for $C_{11}H_{17}O$ $[M+H]^+$ 165.1274, found 165.1279.

R_f = 0.76 (CH_2Cl_2).



212

(*S*)-2-(Adamantan-1-yl)-2-(((*R*)-2-hydroxy-1-phenylethyl)amino)acetonitrile (212): To a mixture of 1-adamantanecarboxaldehyde (**210**) (5.72 g, 34.8 mmol, 1 equiv.) in water (90 mL) was added sodium bisulfite (3.62 g, 34.8 mmol, 1 equiv.), then potassium cyanide (2.27 g, 34.8 mmol, 1 equiv.) at 0 °C. A solution of (*R*)-phenylglycinol (**211**) (4.78 g, 34.8 mmol, 1 equiv.) in MeOH (9 mL) was then added dropwise. The mixture was stirred at r.t. for 2 h then under reflux for 16 h. The mixture was cooled to r.t. and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) to provide the title compound as a white amorphous solid (2.41 g, 7.8 mmol, 22%), m.p. 122-124 °C (lit. m.p.[210] 118-120 °C). Data are consistent with a reported example.[210]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 4 H, H2 and H3), 7.33 – 7.29 (m, 1 H, H1), 4.07 (dd, *J* = 9.2, 3.8 Hz, 1 H, H5), 3.80 (dt, *J* = 10.8, 3.8 Hz, 1 H, H6a), 3.61 – 3.54 (m, 1 H, H6b), 2.87 (s, 1 H, H7), 2.19 (br s, 1 H, OH), 2.04 (s, 3 H, H11), 1.80 – 1.70 (m, 6 H, H10a and H12a), 1.70 – 1.62 (m, 4 H, H12b and NH), 1.61 – 1.54 (m, 3 H, H10b).

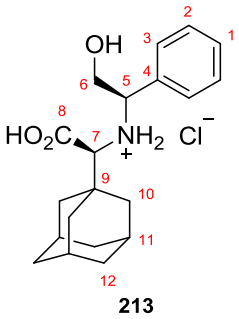
^{13}C NMR (150 MHz, $CDCl_3$): δ 138.7 (C4), 128.9 (C2/C3), 128.4 (C1), 128.0 (C2/C3), 119.3 (C8), 67.8 (C6), 63.3 (C5), 59.3 (C7), 38.9 (C10), 36.9 (C12), 35.9 (C9), 28.3 (C11).

FTIR (ν_{max}, cm^{-1}): 3454 (br w, OH and NH), 2906 (s), 2850 (m), 2359 (w, C≡N), 1454 (m), 1057 (m), 758 (m).

HRMS (ESI): calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$ 311.2118, found 311.2111.

R_f = 0.32 (20% EtOAc/hexane).

$[\alpha]_D^{27.7}$ = -140.4 ($CHCl_3$, *c* = 1.0); lit.[210] $[\alpha]_D^{25}$ = +136.0 (MeOH, *c* = 0.25, for opposite enantiomer).



213

(*R*)-*N*-((*S*)-(Adamantan-1-yl)(carboxy)methyl)-2-hydroxy-1-phenylethan-1-ammonium chloride (213): A mixture of (*S*)-2-(adamantan-1-yl)-2-(((*R*)-2-hydroxy-1-phenylethyl)amino)acetonitrile (**212**) (2.41 g, 7.8 mmol) in 37% aqueous HCl (52 mL) and acetic acid (13 mL) was heated at 80 °C for 16 h. The mixture was then cooled to r.t. then at 0 °C, which resulted in the formation of a white precipitate after several hours. The precipitate was collected by vacuum filtration to provide the title compound as a white crystalline solid (2.06 g, 5.6 mmol, 72%), m.p. >220 °C (dec.) (lit. m.p.[210] 228-230 °C for opposite enantiomer). Data are consistent with a reported example.[210]

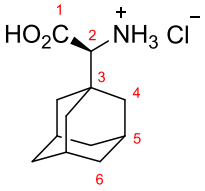
^{1}H NMR (600 MHz, MeOD-d_4): δ 7.57 – 7.48 (m, 5 H, H1, H2 and H3), 4.27 (dd, *J* = 9.0, 4.7 Hz, 1 H, H5), 4.25 – 4.19 (m, 1 H, H6a), 3.98 (dd, *J* = 11.3, 4.7 Hz, 1 H, H6b), 3.20 (s, 1 H, H7), 2.01 (s, 3 H, H11), 1.77 – 1.71 (m, 6 H, H10a and H12a), 1.67 (d, *J* = 11.9 Hz, 3 H, H12b), 1.51 (d, *J* = 11.4 Hz, 3 H, H10b).

^{13}C NMR (150 MHz, MeOD-d_4): δ 169.5 (C8), 132.1 (C4), 131.7 (C1), 130.7 (C2/C3), 130.2 (C2/C3), 69.4 (C7), 67.0 (C5), 62.3 (C6), 39.1 (C10), 37.0 (C12), 36.3 (C9), 29.4 (C11).

FTIR (ν_{max}, cm^{-1}): 3600-2400 (br w, OH and NH), 3386 (br w), 2906 (s), 2851 (m), 1730 (m, C=O), 1556 (m), 1424 (m), 1207 (m), 1052 (m), 763 (m).

HRMS (ESI): calculated for $C_{20}H_{26}NO_3$ [of free base, M-H]$^-$ 328.1918, found 328.1918.

$[\alpha]_D^{27.7}$ = -5.7 (MeOH, *c* = 1.0); lit.[210] $[\alpha]_D^{25}$ = +100.9 (pyridine, *c* = 0.5, for opposite enantiomer).



214

(*S*)-(Adamantan-1-yl)(carboxy)methanammonium chloride (214): A mixture of (*R*)-*N*-((*S*)-(adamantan-1-yl)(carboxy)methyl)-2-hydroxy-1-phenylethan-1-ammonium chloride (**213**) (2.06 g, 5.6 mmol), 20% palladium(II) hydroxide on carbon (0.40 g) and acetic acid (4 mL) in methanol (20 mL) was stirred under H_2 (balloon) at r.t. for 4 d. The mixture was filtered through a pad of Celite, eluting with methanol, then the filtrate evaporated under reduced pressure. The residue was triturated with Et_2O and filtered to provide the title compound as a white crystalline solid (1.40 g, 5.6 mmol, 99%), m.p. >250 °C (dec.) (lit. m.p.[211] 247-292 °C (dec.)). Data are consistent with a reported example.[211]

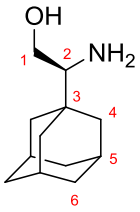
^{1}H NMR (600 MHz, MeOD-d_4): δ 3.53 (s, 1 H, H2), 2.06 (s, 3 H, H5), 1.85 – 1.76 (m, 6 H, H4a and H6a), 1.71 (d, *J* = 11.8 Hz, 3 H, H6b), 1.65 (d, *J* = 12.1 Hz, 3 H, H4b).

^{13}C NMR (150 MHz, MeOD-d_4): δ 170.4 (C1), 63.5 (C2), 39.3 (C4), 37.3 (C6), 35.7 (C3), 29.5 (C5).

FTIR (ν_{max}, cm^{-1}): 3300-2400 (br w, OH and NH), 2890 (s), 2847 (s), 1741 (s, C=O), 1597 (m), 1582 (m), 1499 (s), 1454 (m), 1420 (m), 1374 (w), 1344 (w), 1316 (w), 1291 (w), 1256 (w), 1218 (s), 1201 (m), 1184 (w), 1140 (m), 1118 (m), 1107 (w), 1085 (m), 1035 (m), 976 (w), 938 (w), 911 (w), 858 (m), 832 (m), 815 (m).

HRMS (ESI): calculated for $C_{12}H_{18}NO_2$ [of free base, M-H]$^-$ 208.1343, found 208.1343.

$[\alpha]_D^{27.7}$ = +20.8 (MeOH, *c* = 1.0); lit.[211] $[\alpha]_D^{20}$ = +20.9 (MeOH, *c* = 0.93).



215

(*S*)-2-(Adamantan-1-yl)-2-aminoethan-1-ol (215): To a solution of $LiAlH_4$ (12.3 mL, 1.0 M in THF, 12.3 mmol, 2.2 equiv.) at 0 °C was added slowly portionwise (*S*)-(adamantan-1-yl)(carboxy)methanammonium chloride (**214**) (1.40 g, 5.6 mmol, 1 equiv.). The mixture was then stirred under reflux for 16 h. The mixture was cooled to r.t., quenched slowly with

Na_2SO_4•$10H_2O$ (6 g) and stirred vigorously for 1 h. The mixture was filtered through a pad of Celite, eluting copiously with EtOAc (150 mL). The filtrate was evaporated under reduced pressure to provide the title compound as a white amorphous solid (0.98 g, 5.0 mmol, 90%), m.p. 98-100 °C. Data are consistent with a reported example.[135]

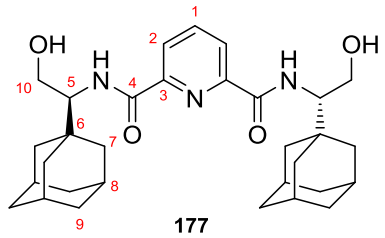
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.69 (dd, *J* = 10.2, 3.8 Hz, 1 H, H1a), 3.24 (t, *J* = 10.2 Hz, 1 H, H1b), 2.32 (dd, *J* = 10.2, 3.8 Hz, 1 H, H2), 2.09 (br s, 3 H, OH and NH_2), 1.96 (s, 3 H, H5), 1.69 (d, *J* = 11.8 Hz, 3 H, H4a), 1.61 (d, *J* = 11.8 Hz, 3 H, H6a), 1.50 (s, 6 H, H4b and H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 62.2 (C1), 61.3 (C2), 38.8 (C4), 37.3 (C6), 35.2 (C3), 28.4 (C5).

FTIR (ν_{max}, cm^{-1}): 3310 (br w, OH and NH), 2904 (m), 2849 (w), 1583 (w), 1450 (w), 1345 (w), 1047 (w), 986 (w), 905 (s), 858 (w).

HRMS (ESI): calculated for $C_{12}H_{22}NO$ $[M+H]^+$ 196.1696, found 196.1702.

$[\alpha]_D^{27.7}$ = +17.6 ($CHCl_3$, *c* = 1.0).



177

***N*^{2},*N*^{6}-Bis((*S*)-1-(adamantan-1-yl)-2-hydroxyethyl)pyridine-2,6-dicarboxamide (177):** To a stirred solution of (*S*)-2-(adamantan-1-yl)-2-aminoethan-1-ol (**215**) (0.488 g, 2.5 mmol, 2 equiv.) and triethylamine (0.35 mL, 2.5 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (13 mL) was added portionwise pyridine-2,6-dicarbonyl chloride (**174**) (0.255 g, 1.25 mmol, 1 equiv.) at 0 °C. The mixture was warmed to r.t. and stirred further for 16 h. Water (10 mL) was added and the organic layer separated. The aqueous layer was extracted further with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 3% → 4% MeOH/CH_2Cl_2) to provide the title compound as a white foam (0.522 g, 1.0 mmol, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.8 Hz, 2 H, H2), 8.07 (br d, *J* = 9.5 Hz, 2 H, NH), 7.93 (t, *J* = 7.8 Hz, 1 H, H1), 3.92 (dd, *J* = 11.0, 3.4 Hz, 2 H, H10a), 3.84 – 3.77 (m,

2 H, H5), 3.73 (dd, *J* = 11.0, 7.1 Hz, 2 H, H10b), 3.16 (br s, 2 H, OH), 1.95 (s, 6 H, H8), 1.70 – 1.58 (m, 24 H, H7 and H9).

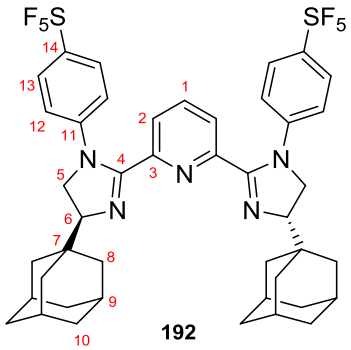
^{13}C NMR (150 MHz, $CDCl_3$): δ 164.4 (C4), 148.7 (C3), 139.2 (C1), 125.1 (C2), 61.7 (C10), 60.3 (C5), 39.3 (C7), 36.9 (C6), 36.0 (C9), 28.3 (C8).

FTIR (ν_{max}, cm^{-1}): 3401 (br w, OH and NH), 2902 (s), 2849 (m), 1727 (w), 1665 (s, C=O), 1528 (s), 1446 (m), 1343 (w), 1316 (w), 1238 (w), 1172 (w), 1105 (w), 1073 (w), 1052 (w), 1031 (w), 1001 (w), 970 (w), 843 (w), 753 (s).

HRMS (ESI): calculated for $C_{31}H_{44}N_3O_4$ $[M+H]^+$ 522.3326, found 522.3309.

R_f = 0.04 (3% MeOH/CH_2Cl_2).

$[\alpha]_D^{25.7}$ = -72.3 ($CHCl_3$, *c* = 1.0).



2,6-Bis((*S*)-4-(adamantan-1-yl)-1-(4-(pentafluorosulfanyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (192): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-(adamantan-1-yl)-2-hydroxyethyl)pyridine-2,6-dicarboxamide (**177**) and 4-(pentafluorothio)aniline (**207**) (0.241 g, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 3% → 5% MeOH/CH_2Cl_2) provided the title compound as a pale yellow gum (319.0 mg, 0.359 mmol, 72%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8 Hz, 2 H, H2), 7.85 (t, *J* = 7.8 Hz, 1 H, H1), 7.36 (d, *J* = 9.0 Hz, 4 H, H13), 6.39 (d, *J* = 9.0 Hz, 4 H, H12), 3.86 (dd, *J* = 10.5, 9.2 Hz, 2 H, H5a), 3.75 (dd, *J* = 10.5, 6.6 Hz, 2 H, H6), 3.66 (dd, *J* = 9.2, 6.6 Hz, 2 H, H5b), 1.97 (s, 6 H, H9), 1.70 (d, *J* = 12.0 Hz, 6 H, H10a), 1.66 – 1.59 (m, 12 H, H8a and H10b), 1.45 (d, *J* = 11.8 Hz, 6 H, H8b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.3 (C4), 148.4 (C3), 147.5 – 147.1 (m, C14), 144.6 (C11), 137.5 (C1), 125.7 (br, C13), 125.5 (C2), 120.3 (C12), 73.7 (C6), 52.7 (C5), 38.3 (C8), 37.2 (C10), 36.2 (C7), 28.3 (C9).

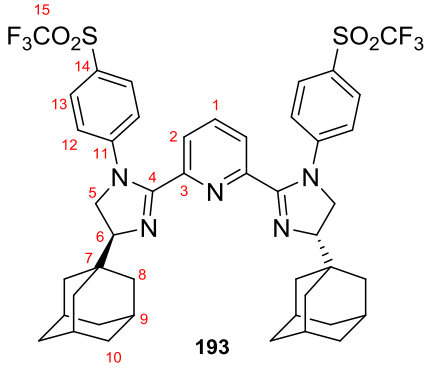
^{19}F NMR (376 MHz, $CDCl_3$): δ 86.4 (qn, *J* = 150.2 Hz, 2 F, SF_{ax}), 64.0 (d, *J* = 150.2 Hz, 8 F, SF_{eq}).

FTIR (ν_{max}, cm^{-1}): 2902 (m), 2849 (w), 1595 (m), 1568 (m), 1506 (m), 1479 (m), 1451 (w), 1430 (w), 1411 (w), 1392 (m), 1334 (w), 1316 (w), 1276 (w), 1245 (w), 1200 (w), 1163 (w), 1136 (w), 1103 (m), 1081 (w), 1008 (w), 907 (m), 822 (s, S-F), 778 (m).

HRMS (ESI): calculated for $C_{43}H_{48}F_{10}N_5S_2$ $[M+H]^+$ 888.3186, found 888.3177.

R_f = 0.28 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{28.5}$ = -126.4 ($CHCl_3$, *c* = 1.0).



2,6-Bis((*S*)-4-(adamantan-1-yl)-1-(4-((trifluoromethyl)sulfonyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (193): Following the general procedure for PyBIM synthesis, using N^2,N^6-bis((*S*)-1-(adamantan-1-yl)-2-hydroxyethyl)pyridine-2,6-dicarboxamide (**177**) and 4-((trifluoromethyl)sulfonyl)aniline (0.248 g, 1.1 mmol, 2.2 equiv.) at 60 °C for 16 h, purified by silica gel column chromatography (eluent: 50% EtOAc/hexane) provided the title compound as a pale yellow foam (284.2 mg, 0.316 mmol, 63%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.9 Hz, 2 H, H2), 7.92 (t, *J* = 7.9 Hz, 1 H, H1), 7.58 (d, *J* = 8.9 Hz, 4 H, H13), 6.50 (d, *J* = 8.9 Hz, 4 H, H12), 3.83 (dd, *J* = 9.8, 8.0 Hz, 2 H, H5a), 3.81 – 3.77 (m, 2 H, H6), 3.74 (dd, *J* = 8.0, 6.3 Hz, 2 H, H5b), 1.96 (s, 6 H, H9), 1.68 (d, *J* = 11.9 Hz, 6 H, H10a), 1.65 – 1.56 (m, 12 H, H8a and H10b), 1.44 (d, *J* = 12.0 Hz, 6 H, H8b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.2 (C4), 148.6 (C11), 148.1 (C3), 138.0 (C1), 130.8 (C13), 125.7 (C2), 121.3 (C14), 120.2 (C12), 119.9 (q, *J* = 325.7 Hz, C15), 73.9 (C6), 52.2 (C5), 38.3 (C8), 37.0 (C10), 36.1 (C7), 28.1 (C9).

^{19}F NMR (376 MHz, $CDCl_3$): δ -78.7 (s, 6 F, F15).

FTIR (ν_{max}, cm^{-1}): 2904 (m), 2850 (w), 1586 (m), 1568 (w), 1501 (w), 1476 (w), 1411 (w), 1363 (m), 1315 (w), 1303 (w), 1276 (w), 1246 (w), 1215 (s), 1193 (m), 1140 (s), 1076 (m), 1039 (w), 1005 (w), 905 (s), 830 (m), 792 (w), 764 (w).

HRMS (ESI): calculated for $C_{45}H_{48}F_6N_5O_4S_2$ $[M+H]^+$ 900.3046, found 900.3045.

$\boldsymbol{R_f}$ = 0.37 (50% EtOAc/hexane).

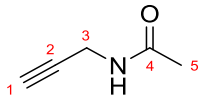
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28.5}}$ = -136.3 ($CHCl_3$, *c* = 1.0).

5.3.3. Synthetic procedures and characterisation for alkyne starting materials

General procedure for propargylamide synthesis *via* EDC coupling: To a solution of the appropriate carboxylic acid (5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added, if stated, DIPEA (1.05 mL, 6.0 mmol, 1.2 equiv.). EDC hydrochloride (1.15 g, 6.0 mmol, 1.2 equiv.) was added and stirred for 2 min, then HOBt (0.743 g, 5.5 mmol, 1.1 equiv.) was added and stirred for a further 2 min. Propargylamine (0.35 mL, 5.5 mmol, 1.1 equiv.) was then added and the mixture stirred at r.t. for 16 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous Na_2CO_3 solution (25 mL) then 1 M aqueous HCl solution (20 mL). The organic phase was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to provide the desired propargylamide.

General procedure for propargylamide synthesis *via* acyl chlorides: To a solution of the propargylamine (0.35 mL, 5.5 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL) was added Et_3N (0.77 mL, 5.5 mmol, 1.1 equiv.) and DMAP (61.1 mg, 0.5 mmol, 0.1 equiv.). The appropriate acyl chloride (5.0 mmol, 1.0 equiv.) was then added (dropwise if liquid, as a solution in 2 mL CH_2Cl_2 if solid) and the mixture stirred at r.t. for 16 h. The mixture was diluted with CH_2Cl_2 (10 mL) and treated with 1 M aqueous NaOH solution (20 mL). The organic layer was separated and the aqueous layer extracted further with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated under reduced pressure. The residue was purified by silica gel column chromatography to provide the desired propargylamide.

4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60): Prepared as described previously (Section 5.2.1).



***N*-(Prop-2-yn-1-yl)acetamide:** Following the general procedure for propargylamide synthesis *via* acyl chlorides using acetyl chloride (0.35 mL, 5.0 mmol), purified by silica gel column chromatography (eluent: 35% EtOAc/CH_2Cl_2) provided the title compound as a yellow crystalline solid (0.271 g, 2.79 mmol, 56%), m.p. 89-90 °C (lit. m.p.[212] 83-85 °C). Data are consistent with a reported example.[213]

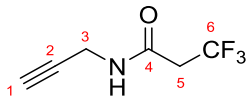
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.97 (br s, 1 H, NH), 4.03 (dd, *J* = 5.3, 2.5 Hz, 2 H, H3), 2.22 (t, *J* = 2.6 Hz, 1 H, H1), 2.00 (s, 3 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.0 (C4), 79.7 (C2), 71.6 (C1), 29.4 (C3), 23.1 (C5).

FTIR (ν_{max}, cm^{-1}): 3293 (m, NH and alkyne CH), 3072 (w), 2922 (m), 2851 (w), 1644 (s, C=O), 1544 (s), 1423 (m), 1374 (m), 1287 (m), 1099 (w), 1029 (w), 927 (w).

HRMS (ESI): calculated for C_5H_7NONa $[M+Na]^+$ 120.0420, found 120.0425.

***R*$_f$** = 0.23 (35% EtOAc/CH_2Cl_2).



3,3,3-Trifluoro-*N*-(prop-2-yn-1-yl)propanamide: Following the general procedure for propargylamide synthesis *via* acyl chlorides using 3,3,3-trifluoropropionyl chloride (1.54 mL, 15.0 mmol), purified by silica gel column chromatography (eluent: 35% EtOAc/hexane) provided the title compound as a white crystalline solid (1.66 g, 10.1 mmol, 67%), m.p. 76-77 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.89 (br s, 1 H, NH), 4.06 (dd, *J* = 5.3, 2.6 Hz, 2 H, H3), 3.13 (q, *J* = 10.5 Hz, 2 H, H5), 2.25 (t, *J* = 2.5 Hz, 1 H, H1).

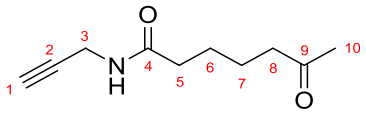
^{13}C NMR (150 MHz, $CDCl_3$): δ 163.2 (q, *J* = 3.5 Hz, C4), 124.0 (q, *J* = 276.7 Hz, C6), 78.7 (C2), 72.1 (C1), 41.2 (q, *J* = 29.6 Hz, C5), 29.6 (C3).

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.1 (s, 3 F, F6).

FTIR (ν_{max}, cm^{-1}): 3317 (m, NH), 3302 (m, alkyne CH), 3098 (w), 1661 (s, C=O), 1567 (m), 1427 (m), 1373 (m), 1349 (w), 1311 (w), 1262 (s), 1242 (s), 1132 (m), 1106 (m), 1057 (m), 1035 (w), 928 (m), 854 (w), 778 (w).

HRMS (ESI): calculated for $C_6H_7F_3NO$ $[M+H]^+$ 166.0474, found 166.0468.

***R*$_f$** = 0.32 (35% EtOAc/hexane).



6-Oxo-*N*-(prop-2-yn-1-yl)heptanamide: Following the general procedure for propargylamide synthesis *via* EDC coupling using 6-oxoheptanoic acid (0.800 g, 5.0 mmol, 90% purity), purified by silica gel column chromatography (eluent: 90% EtOAc/hexane)

provided the title compound as a white crystalline solid (0.471 g, 2.60 mmol, 52%), m.p. 89-91 °C (lit. m.p.[214] 88-90 °C). Data are consistent with a reported example.[214]

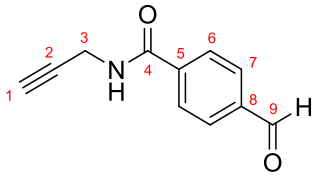
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.83 (br s, 1 H, NH), 4.05 (dd, *J* = 5.2, 2.5 Hz, 2 H, H3), 2.47 (t, *J* = 6.7 Hz, 2 H, H8), 2.23 – 2.19 (m, 3 H, H1 and H5), 2.14 (s, 3 H, H10), 1.67 – 1.56 (m, 4 H, H6 and H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.0 (C9), 172.3 (C4), 79.7 (C2), 71.7 (C1), 43.4 (C8), 36.2 (C5), 30.1 (C10), 29.3 (C3), 25.0 (C6/C7), 23.2 (C6/C7).

FTIR (ν_{max}, cm^{-1}): 3284 (s, NH and alkyne CH), 3078 (w), 2933 (w), 2862 (w), 1711 (m, C=O), 1703 (m), 1640 (s, C=O), 1556 (w), 1466 (w), 1424 (w), 1376 (w), 1358 (w), 1272 (w), 1241 (w), 1168 (w), 1106 (w), 1017 (w), 924 (w), 880 (w).

HRMS (ESI): calculated for $C_{10}H_{16}NO_2$ $[M+H]^+$ 188.1176, found 188.1183.

***R*$_f$** = 0.45 (90% EtOAc/hexane).



4-Formyl-*N*-(prop-2-yn-1-yl)benzamide: Following the general procedure for propargylamide synthesis *via* EDC coupling using 4-formylbenzoic acid (0.751 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 50% EtOAc/hexane) provided the title compound as a white amorphous solid (0.444 g, 2.37 mmol, 47%), m.p. 171-172 °C. Data are consistent with a reported example.[215]

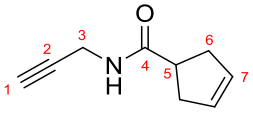
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.08 (s, 1 H, H9), 7.96 (d, *J* = 8.5 Hz, 2 H, H7), 7.94 (d, *J* = 8.5 Hz, 2 H, H6), 6.39 (br s, 1 H, NH), 4.28 (dd, *J* = 5.2, 2.6 Hz, 2 H, H3), 2.31 (t, *J* = 2.6 Hz, 1 H, H1).

^{13}C NMR (150 MHz, $CDCl_3$): δ 191.6 (C9), 166.1 (C4), 138.9 (C5), 138.6 (C8), 130.0 (C7), 127.9 (C6), 79.1 (C2), 72.5 (C1), 30.2 (C3).

FTIR (ν_{max}, cm^{-1}): 3316 (m, NH and alkyne CH), 3247 (w), 1712 (m, C=O), 1642 (s, C=O), 1540 (m), 1501 (w), 1416 (w), 1299 (w), 1259 (w), 1210 (w), 850 (w), 757 (w).

HRMS (ESI): calculated for $C_{11}H_{10}NO_2$ $[M+H]^+$ 188.0706, found 188.0704.

***R*$_f$** = 0.41 (50% EtOAc/hexane).



***N*-(Prop-2-yn-1-yl)cyclopent-3-ene-1-carboxamide:** Following the general procedure for propargylamide synthesis *via* EDC coupling using 3-cyclopentene-1-carboxylic acid (0.561 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) provided the title compound as a white amorphous solid (0.518 g, 3.47 mmol, 69%), m.p. 102-104 °C (lit. m.p.[216] 105-107 °C). Data are consistent with a reported example.[216]

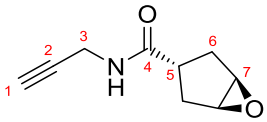
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.69 (s, 2 H, H7), 5.63 (br s, 1 H, NH), 4.07 (dd, *J* = 5.2, 2.5 Hz, 2 H, H3), 2.96 (qn, *J* = 8.0 Hz, 1 H, H5), 2.64 (d, *J* = 8.0 Hz, 4 H, H6), 2.23 (t, *J* = 2.5 Hz, 1 H, H1).

^{13}C NMR (150 MHz, $CDCl_3$): δ 175.6 (C4), 129.4 (C7), 79.8 (C2), 71.7 (C1), 43.4 (C5), 37.0 (C6), 29.5 (C3).

FTIR (ν_{max}, cm^{-1}): 3278 (m, NH and alkyne CH), 3062 (w), 2914 (w), 2848 (w), 1634 (s, C=O), 1618 (m), 1538 (m), 1440 (w), 1388 (w), 1343 (w), 1299 (w), 1234 (m), 1182 (w), 1039 (w), 948 (w), 847 (w).

HRMS (ESI): calculated for $C_9H_{12}NO$ $[M+H]^+$ 150.0913, found 150.0919.

***R*$_f$** = 0.39 (40% EtOAc/hexane).



(1*R*,3*s*,5*S*)-*N*-(Prop-2-yn-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide: To a solution of *N*-(prop-2-yn-1-yl)cyclopent-3-ene-1-carboxamide (0.298 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) at 0 °C was added *m*-CPBA (0.583 g, 2.6 mmol, 1.3 equiv., 77% purity) portionwise. The mixture was then stirred at r.t. for 4 h. The mixture was filtered to remove precipitated *m*-chlorobenzoic acid, washed once on the filter with CH_2Cl_2 (1 mL), then the filtrate washed with saturated aqueous Na_2CO_3 solution. The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and purified by silica gel column chromatography (eluent: 80% EtOAc/hexane) to provide the title compound *trans*-epoxide as a white amorphous solid (0.143 g, 0.87 mmol, 43%), m.p. 133-135 °C.

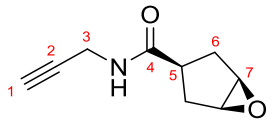
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.71 (br s, 1 H, NH), 4.04 (dd, *J* = 5.2, 2.6 Hz, 2 H, H3), 3.53 (s, 2 H, H7), 2.40 (tt, *J* = 9.6, 7.9 Hz, 1 H, H5), 2.26 (dd, *J* = 14.0, 7.9 Hz, 2 H, H6a), 2.23 (t, *J* = 2.6 Hz, 1 H, H1), 1.96 (dd, *J* = 14.0, 9.6 Hz, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.7 (C4), 79.5 (C2), 71.9 (C1), 56.6 (C7), 38.9 (C5), 31.9 (C6), 29.5 (C3).

FTIR (ν_{max}, cm^{-1}): 3286 (m, NH), 3230 (m, alkyne CH), 3050 (w), 2926 (w), 1635 (s, C=O), 1544 (m), 1446 (w), 1391 (w), 1294 (w), 1243 (w), 1224 (w), 1059 (w), 1035 (w), 958 (w), 832 (m).

HRMS (ESI): calculated for $C_9H_{12}NO_2$ $[M+H]^+$ 166.0863, found 166.0871.

***R*$_f$** = 0.52 (80% EtOAc/hexane).



(1*R*,3*r*,5*S*)-*N*-(Prop-2-yn-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide: Following the epoxidation of *N*-(prop-2-yn-1-yl)cyclopent-3-ene-1-carboxamide, the *cis*-epoxide was also isolated as a white amorphous solid (0.149 g, 0.90 mmol, 45%), m.p. 114-116 °C.

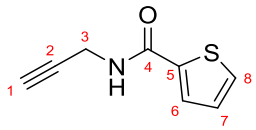
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (br s, 1 H, NH), 3.95 (dd, *J* = 5.3, 2.5 Hz, 2 H, H3), 3.64 (s, 2 H, H7), 2.96 (tt, *J* = 10.3, 1.3 Hz, 1 H, H5), 2.23 (dd, *J* = 15.5, 1.3 Hz, 2 H, H6a), 2.19 (t, *J* = 2.5 Hz, 1 H, H1), 2.15 (dd, *J* = 15.5, 10.3 Hz, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.2 (C4), 80.1 (C2), 71.2 (C1), 59.1 (C7), 42.5 (C5), 32.1 (C6), 29.3 (C3).

FTIR (ν_{max}, cm^{-1}): 3287 (m, NH and alkyne CH), 3038 (w), 2929 (w), 1652 (s, C=O), 1528 (s), 1431 (w), 1402 (w), 1352 (w), 1306 (w), 1243 (m), 1195 (w), 1100 (w), 1063 (w), 1010 (w), 948 (w), 921 (w), 889 (w), 841 (s).

HRMS (ESI): calculated for $C_9H_{12}NO_2$ $[M+H]^+$ 166.0863, found 166.0870.

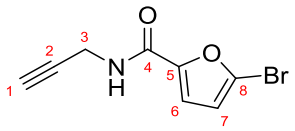
***R*$_f$** = 0.30 (80% EtOAc/hexane).



***N*-(Prop-2-yn-1-yl)thiophene-2-carboxamide:** Following the general procedure for propargylamide synthesis *via* EDC coupling using 2-thiophenecarboxylic acid (0.641 g,

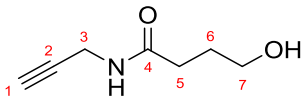
5.0 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as an off-white amorphous solid (0.690 g, 4.17 mmol, 83%), m.p. 117-119 °C (lit. m.p.[216] 109-111 °C). Data are consistent with a reported example.[217]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 3.8, 1.0 Hz, 1 H, H6), 7.49 (dd, *J* = 5.0, 1.0 Hz, 1 H, H8), 7.08 (dd, *J* = 5.0, 3.8 Hz, 1 H, H7), 6.21 (br s, 1 H, NH), 4.24 (dd, *J* = 5.3, 2.5 Hz, 2 H, H3), 2.28 (t, *J* = 2.5 Hz, 1 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 161.6 (C4), 138.1 (C5), 130.5 (C8), 128.7 (C6), 127.8 (C7), 79.4 (C2), 72.1 (C1), 29.8 (C3).
FTIR (ν_{max}, cm^{-1}): 3289 (s, NH and alkyne CH), 3108 (w), 3085 (w), 3051 (w), 1626 (s, C=O), 1549 (s), 1516 (w), 1414 (m), 1358 (w), 1344 (w), 1310 (m), 1264 (w), 1248 (w), 1148 (w), 1062 (w), 1041 (w), 963 (w), 911 (w), 860 (w), 790 (w), 752 (w).
HRMS (ESI): calculated for C_8H_8NOS $[M+H]^+$ 166.0321, found 166.0324.
***R*$_f$** = 0.40 (40% EtOAc/hexane).



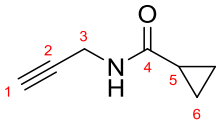
5-Bromo-*N*-(prop-2-yn-1-yl)furan-2-carboxamide: Following the general procedure for propargylamide synthesis *via* EDC coupling using 5-bromo-2-furoic acid (0.995 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a white crystalline solid (0.900 g, 3.95 mmol, 79%), m.p. 105-107 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, *J* = 3.5 Hz, 1 H, H6), 6.47 (br s, 1 H, NH), 6.45 (d, *J* = 3.5 Hz, 1 H, H7), 4.21 (dd, *J* = 5.5, 2.5 Hz, 2 H, H3), 2.28 (t, *J* = 2.5 Hz, 1 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 156.8 (C4), 149.1 (C5), 124.9 (C8), 117.3 (C6), 114.4 (C7), 79.1 (C2), 72.2 (C1), 29.1 (C3).
FTIR (ν_{max}, cm^{-1}): 3299 (m, NH and alkyne CH), 3122 (w), 1650 (s, C=O), 1596 (m), 1574 (w), 1523 (s), 1469 (s), 1422 (w), 1352 (w), 1298 (m), 1204 (w), 1172 (w), 1126 (w), 1054 (w), 1014 (w), 938 (w), 925 (w), 799 (w), 753 (w).
HRMS (ESI): calculated for $C_8H_7NO_2Br$ $[M+H]^+$ 227.9655, found 227.9650.
***R*$_f$** = 0.53 (40% EtOAc/hexane).



4-Hydroxy-*N*-(prop-2-yn-1-yl)butanamide: A neat mixture of γ-butyrolactone (0.77 mL, 10.0 mmol, 1 equiv.) and propargylamine (0.96 mL, 15.0 mmol, 1.5 equiv.) in a 5 mL microwave vial were heated at 120 °C for 3 h. The mixture was then purified directly by silica gel column chromatography (eluent: EtOAc) to provide the title compound as a pale orange amorphous solid (0.994 g, 7.03 mmol, 70%), m.p. 37-40 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.11 (br s, 1 H, NH), 4.05 (dd, *J* = 5.3, 2.6 Hz, 2 H, H3), 3.72 – 3.68 (m, 2 H, H7), 2.77 (br s, 1 H, OH), 2.37 (t, *J* = 6.9 Hz, 2 H, H5), 2.23 (t, *J* = 2.6 Hz, 1 H, H1), 1.93 – 1.86 (m, 2 H, H6).
^{13}C NMR (150 MHz, $CDCl_3$): δ 173.2 (C4), 79.6 (C2), 71.8 (C1), 62.3 (C7), 33.6 (C5), 29.4 (C3), 28.0 (C6).
FTIR (ν_{max}, cm^{-1}): 3600-3200 (br m, OH), 3276 (m, NH and alkyne CH), 2941 (w), 1634 (s, C=O), 1544 (s), 1423 (m), 1339 (w), 1262 (m), 1168 (w), 1038 (m), 928 (w).
HRMS (ESI): calculated for $C_7H_{12}NO_2$ $[M+H]^+$ 142.0863, found 142.0868.
***R*$_f$** = 0.19 (EtOAc).



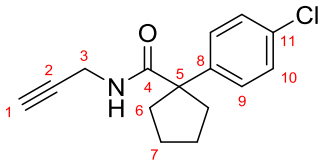
***N*-(Prop-2-yn-1-yl)cyclopropanecarboxamide:** Following the general procedure for propargylamide synthesis *via* acyl chlorides using cyclopropanecarbonyl chloride (0.14 mL, 1.5 mmol), purified by silica gel column chromatography (eluent: 35% EtOAc/hexane) provided the title compound as a white crystalline solid (85.8 mg, 0.697 mmol, 46%), m.p. 70-71 °C (lit. m.p.[216] 64-66 °C). Data are consistent with a reported example.[216]

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.83 (br s, 1 H, NH), 4.08 (dd, *J* = 5.3, 2.5 Hz, 2 H, H3), 2.23 (t, *J* = 2.5 Hz, 1 H, H1), 1.39 – 1.32 (m, 1 H, H5), 1.02 – 0.97 (m, 2 H, H6a), 0.80 – 0.73 (m, 2 H, H6b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 173.8 and 173.7 (rotameric, C4), 79.9 (C2), 71.31 and 71.29 (rotameric, C1), 29.3 (C3), 14.48 and 14.46 (rotameric, C5), 7.4 (C6).

FTIR (ν_{max}, cm^{-1}): 3293 (m, NH and alkyne CH), 3064 (w), 3013 (w), 2924 (w), 1799 (w), 1727 (w), 1643 (s, C=O), 1537 (w), 1449 (m), 1421 (m), 1401 (m), 1349 (m), 1237 (s), 1197 (m), 1104 (m), 1061 (m), 1032 (m), 1012 (m), 931 (m), 896 (m), 825 (w).

HRMS (ESI): calculated for $C_7H_{10}NO$ $[M+H]^+$ 124.0757, found 124.0754.

***R*$_f$** = 0.26 (35% EtOAc/hexane).



1-(4-Chlorophenyl)-*N*-(prop-2-yn-1-yl)cyclopentane-1-carboxamide: Following the general procedure for propargylamide synthesis *via* acyl chlorides using 1-(4-chlorophenyl)-1-cyclopentanecarbonyl chloride (1.22 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) provided the title compound as a white amorphous solid (0.909 g, 3.47 mmol, 69%), m.p. 123-124 °C.

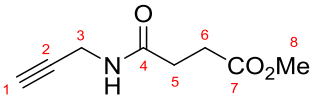
^{1}H NMR (600 MHz, CDCl$_3$): δ 7.30 (d, *J* = 8.7 Hz, 2 H, H10), 7.27 (d, *J* = 8.7 Hz, 2 H, H9), 5.40 (br s, 1 H, NH), 3.92 (dd, *J* = 5.3, 2.5 Hz, 2 H, H3), 2.47 – 2.40 (m, 2 H, H6a), 2.14 (t, *J* = 2.5 Hz, 1 H, H1), 2.00 – 1.93 (m, 2 H, H6b), 1.83 – 1.77 (m, 2 H, H7a), 1.69 – 1.62 (m, 2 H, H7b).

^{13}C NMR (150 MHz, CDCl$_3$): δ 175.7 (C4), 142.3 (C11), 133.0 (C8), 129.0 (C10), 128.3 (C9), 79.5 (C2), 71.6 (C1), 58.8 (C5), 36.9 (C6), 29.7 (C3), 23.9 (C7).

FTIR (ν_{max}, cm^{-1}): 3306 (m, NH), 3286 (m, alkyne CH), 2957 (m), 2925 (m), 2874 (m), 1694 (m), 1637 (s, C=O), 1594 (w), 1526 (s), 1491 (m), 1462 (m), 1416 (m), 1401 (w), 1343 (w), 1275 (m), 1256 (m), 1219 (w), 1177 (w), 1093 (m), 1013 (m), 949 (w), 920 (w), 898 (w), 875 (w), 831 (m), 773 (w), 761 (w).

HRMS (ESI): calculated for $C_{15}H_{17}NOCl$ $[M+H]^+$ 262.0993, found 262.0990.

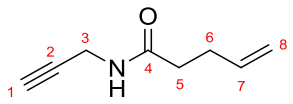
***R*$_f$** = 0.38 (30% EtOAc/hexane).



Methyl 4-oxo-4-(prop-2-yn-1-ylamino)butanoate: Following the general procedure for propargylamide synthesis *via* acyl chlorides using methyl 4-chloro-4-oxobutyrate (0.37 mL, 3.0 mmol), purified by silica gel column chromatography (eluent: 35% → 50%

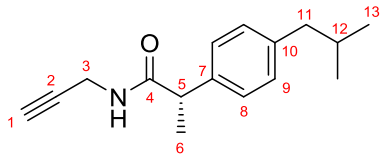
EtOAc/hexane) provided the title compound as a yellow crystalline solid (0.334 g, 1.97 mmol, 66%), m.p. 48-49 °C (lit. m.p.[218] 44-46 °C). Data are consistent with a reported example.[218]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.00 (br s, 1 H, NH), 3.89 (dd, *J* = 5.5, 2.6 Hz, 2 H, H3), 3.54 (s, 3 H, H8), 2.53 (t, *J* = 7.1 Hz, 2 H, H6), 2.42 (t, *J* = 7.1 Hz, 2 H, H5), 2.14 (t, *J* = 2.6 Hz, 1 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 173.2 (C7), 171.4 (C4), 79.6 (C2), 71.1 (C1), 51.6 (C8), 30.3 (C6), 29.0 (C3/C5), 28.9 (C3/C5).
FTIR (ν_{max}, cm^{-1}): 3287 (m, NH and alkyne CH), 2955 (w), 2924 (w), 2851 (w), 1732 (s, C=O), 1651 (s, C=O), 1535 (s), 1438 (m), 1363 (m), 1201 (s), 1167 (s), 1089 (w), 1026 (m), 992 (w), 922 (w), 847 (w), 801 (w).
HRMS (ESI): calculated for $C_8H_{12}NO_3$ $[M+H]^+$ 170.0812, found 170.0816.
***R*$_f$** = 0.10 (35% EtOAc/hexane).



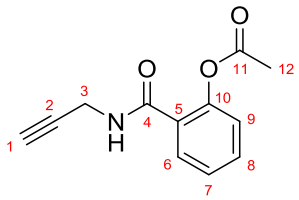
***N*-(Prop-2-yn-1-yl)pent-4-enamide:** Following the general procedure for propargylamide synthesis *via* EDC coupling using 4-pentenoic acid (0.20 mL, 2.0 mmol), purified by silica gel column chromatography (eluent: 35% EtOAc/hexane) provided the title compound as a yellow oil (0.149 g, 1.09 mmol, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.82 (br s, 1 H, NH), 5.75 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1 H, H7), 4.99 (dd, *J* = 17.1, 1.5 Hz, 1 H, $H8_{trans}$), 4.92 (dd, *J* = 10.2, 1.5 Hz, 1 H, $H8_{cis}$), 3.96 (dd, *J* = 5.4, 2.6 Hz, 2 H, H3), 2.35 – 2.29 (m, 2 H, H6), 2.29 – 2.24 (m, 2 H, H5), 2.16 (t, *J* = 2.6 Hz, 1 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6 (C4), 136.8 (C7), 115.5 (C8), 79.7 (C2), 71.2 (C1), 35.3 (C5), 29.4 (C6), 29.0 (C3).
FTIR (ν_{max}, cm^{-1}): 3293 (m, NH and alkyne CH), 3078 (w), 2924 (w), 2855 (w), 1639 (s, C=O), 1536 (s), 1421 (m), 1343 (w), 1266 (m), 1194 (w), 1117 (w), 1031 (w), 996 (w), 915 (m).
HRMS (ESI): calculated for $C_8H_{12}NO$ $[M+H]^+$ 138.0913, found 138.0914.
***R*$_f$** = 0.22 (35% EtOAc/hexane).



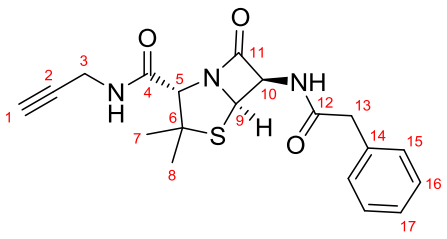
(*S*)-2-(4-Isobutylphenyl)-*N*-(prop-2-yn-1-yl)propanamide: Following the general procedure for propargylamide synthesis *via* EDC coupling using (*S*)-ibuprofen (1.072 g, 5.2 mmol), purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a white crystalline solid (1.071 g, 4.40 mmol, 85%), m.p. 75-76 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.0 Hz, 2 H, H8), 7.12 (d, *J* = 8.0 Hz, 2 H, H9), 5.66 (br s, 1 H, NH), 4.03 (ddd, *J* = 17.6, 5.5, 2.5 Hz, 1 H, H3a), 3.92 (ddd, *J* = 17.6, 5.1, 2.5 Hz, 1 H, H3b), 3.55 (q, *J* = 7.2 Hz, 1 H, H5), 2.45 (d, *J* = 7.2 Hz, 2 H, H11), 2.16 (t, *J* = 2.5 Hz, 1 H, H1), 1.89 – 1.81 (m, 1 H, H12), 1.51 (d, *J* = 7.2 Hz, 3 H, H6), 0.90 (d, *J* = 6.7 Hz, 6 H, H13).
^{13}C NMR (150 MHz, $CDCl_3$): δ 174.2 (C4), 141.0 (C10), 138.2 (C7), 129.8 (C9), 127.5 (C8), 79.7 (C2), 71.5 (C1), 46.6 (C5), 45.1 (C11), 30.3 (C12), 29.5 (C3), 22.5 (C13), 18.6 (C6).
FTIR (ν_{max}, cm^{-1}): 3292 (m, NH and alkyne CH), 2955 (m), 2928 (m), 2869 (w), 1650 (s, C=O), 1537 (m), 1512 (m), 1465 (w), 1421 (w), 1366 (w), 1230 (w), 1073 (w), 1016 (w), 923 (w), 851 (w).
HRMS (ESI): calculated for $C_{16}H_{21}NONa$ $[M+Na]^+$ 266.1515, found 266.1502.
R_f = 0.29 (25% EtOAc/hexane).
$[\alpha]_D^{25.0}$ = +3.0 ($CHCl_3$, *c* = 1.0).



2-(Prop-2-yn-1-ylcarbamoyl)phenyl acetate: Following the general procedure for propargylamide synthesis *via* EDC coupling using aspirin (0.901 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) then trituration with Et_2O (1 mL) provided the title compound as a white crystalline solid (0.408 g, 1.88 mmol, 38%), m.p. 91-92 °C (lit. m.p.[219] 86-88 °C). Data are consistent with a reported example.[219]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 8.0, 1.6 Hz, 1 H, H6), 7.47 (td, *J* = 8.0, 1.6 Hz, 1 H, H8), 7.30 (td, *J* = 8.0, 1.0 Hz, 1 H, H7), 7.11 (dd, *J* = 8.0, 1.0 Hz, 1 H, H9), 6.58 (br s, 1 H, NH), 4.19 (dd, *J* = 5.2, 2.6 Hz, 2 H, H3), 2.35 (s, 3 H, H12), 2.28 (t, *J* = 2.6 Hz, 1 H, H1).
^{13}C NMR (150 MHz, $CDCl_3$): δ 169.1 (C11), 165.1 (C4), 148.1 (C10), 132.2 (C8), 130.2 (C6), 127.5 (C5), 126.5 (C7), 123.4 (C9), 79.5 (C2), 72.1 (C1), 29.7 (C3), 21.1 (C12).
FTIR (ν_{max}, cm^{-1}): 3287 (w, NH and alkyne CH), 1766 (m, C=O), 1649 (m, C=O), 1608 (m), 1521 (m), 1481 (m), 1448 (w), 1424 (w), 1370 (m), 1302 (m), 1191 (s), 1101 (m), 1046 (w), 1012 (w), 988 (w), 955 (w), 913 (w), 874 (w), 833 (w), 788 (w), 751 (w).
HRMS (ESI): calculated for $C_{12}H_{11}NO_3Na$ $[M+Na]^+$ 240.0631, found 240.0621.
R_f = 0.14 (30% EtOAc/hexane).



(2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-*N*-(prop-2-yn-1-yl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide: Penicillin G sodium salt (1.43 g, 4.0 mmol) was dissolved in 1 M HCl aqueous solution (30 mL) and then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to provide the carboxylic acid. Then, following the general procedure for propargylamide synthesis *via* EDC coupling using penicillin G (1.34 g, 4.0 mmol) and DMAP (48.9 mg, 0.4 mmol) as additive, purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a pale yellow amorphous solid (0.570 g, 1.53 mmol, 38%), m.p. 140-142 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.4 Hz, 2 H, H16), 7.30 (t, *J* = 7.4 Hz, 1 H, H17), 7.24 (d, *J* = 7.4 Hz, 2 H, H15), 6.79 (br t, *J* = 5.2 Hz, 1 H, C3-NH), 6.24 (br d, *J* = 9.2 Hz, 1 H, C10-NH), 5.73 (dd, *J* = 9.2, 4.5 Hz, 1 H, H10), 5.36 (d, *J* = 4.5 Hz, 1 H, H9), 4.11 (s, 1 H, H5), 4.07 (ddd, *J* = 17.6, 5.9, 2.5 Hz, 1 H, H3a), 3.92 (ddd, *J* = 17.6, 5.0, 2.5 Hz, 1 H, H3b), 3.64 – 3.56 (m, 2 H, H13), 2.23 (t, *J* = 2.5 Hz, 1 H, H1), 1.66 (s, 3 H, H7/H8), 1.48 (s, 3 H, H7/H8).

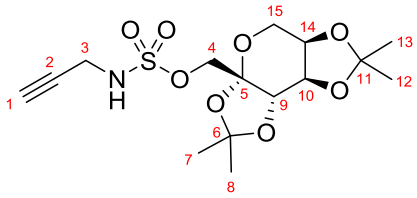
^{13}C NMR (150 MHz, $CDCl_3$): δ 176.4 (C11), 170.7 (C12), 167.2 (C4), 133.7 (C14), 129.5 (C15), 129.2 (C16), 127.8 (C17), 78.9 (C2), 72.4 (C5), 72.1 (C1), 66.4 (C9), 65.0 (C6), 57.4 (C10), 43.3 (C13), 29.1 (C3), 28.5 (C7/C8), 26.6 (C7/C8).

FTIR (ν_{max}, cm^{-1}): 3287 (m, NH and alkyne CH), 3061 (w), 2969 (w), 2932 (w), 1781 (m, C=O), 1654 (s, C=O), 1605 (w), 1525 (m), 1455 (w), 1422 (w), 1390 (w), 1371 (w), 1292 (m), 1238 (m), 1160 (w), 1130 (w), 1058 (w), 1031 (w), 939 (w), 893 (w).

HRMS (ESI): calculated for $C_{19}H_{22}N_3O_3S$ $[M+H]^+$ 372.1376, found 372.1387.

R_f = 0.24 (50% EtOAc/hexane).

$[\alpha]_D^{25.0}$ = +228.6 ($CHCl_3$, *c* = 1.0).



((3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3a-yl)methyl prop-2-yn-1-ylsulfamate: To a solution of topiramate (1.12 g, 3.3 mmol, 1 equiv.) in CH_2Cl_2 (6 mL) was added DMAP (4.0 mg, 0.033 mmol, 0.01 equiv.), Et_3N (0.51 mL, 3.63 mmol, 1.1 equiv.) and Boc anhydride (0.83 mL, 3.63 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 16 h, then evaporated under reduced pressure to provide crude mono-Boc protected topiramate. The residue was redissolved in anhydrous THF (20 mL), then cooled to 0 °C. Triphenylphosphine (1.57 g, 6.0 mmol, 1.8 equiv.) and propargyl alcohol (0.35 mL, 6.0 mmol, 1.8 equiv.) were added, followed by dropwise addition of diisopropyl azodicarboxylate (1.18 mL, 6.0 mmol, 1.8 equiv.) over *ca*. 15 min. The mixture was warmed to r.t. and stirred further for 16 h. The mixture was then evaporated under reduced pressure then the residue triturated with Et_2O (25 mL). The triphenylphosphine oxide byproduct was filtered off, washed on the filter with Et_2O (25 mL) then the filtrate evaporated under reduced pressure. The residue was redissolved in CH_2Cl_2 (20 mL) then trifluoroacetic acid (4.8 mL, 50.0 mmol, 15.0 equiv.) was added and the mixture stirred at r.t. for 16 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and the organic layer separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:

10% Et_2O/CH_2Cl_2) to provide the title compound as a colourless gum (0.375 g, 0.99 mmol, 30% over three steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.84 (br t, *J* = 5.7 Hz, 1 H, NH), 4.61 (dd, *J* = 7.9, 2.6 Hz, 1 H, H10), 4.33 (d, *J* = 2.6 Hz, 1 H, H9), 4.26 (d, *J* = 10.6 Hz, 1 H, H4a), 4.24 (ddd, *J* = 7.9, 1.9, 0.7 Hz, 1 H, H14), 4.18 (d, *J* = 10.6 Hz, 1 H, H4b), 4.00 – 3.91 (m, 2 H, H3), 3.91 (dd, *J* = 13.0, 1.9 Hz, 1 H, H15a), 3.78 (dd, *J* = 13.0, 0.7 Hz, 1 H, H15b), 2.37 (t, *J* = 2.5 Hz, 1 H, H1), 1.55 (s, 3 H, H7/H8), 1.48 (s, 3 H, H12/H13), 1.42 (s, 3 H, H7/H8), 1.34 (s, 3 H, H12/H13).

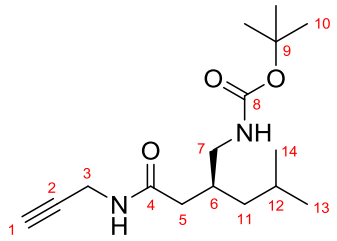
^{13}C NMR (150 MHz, $CDCl_3$): δ 109.5 (C6), 109.4 (C11), 100.9 (C5), 78.0 (C2), 73.8 (C1), 70.9 (C14), 70.7 (C4), 70.5 (C9), 70.0 (C10), 61.5 (C15), 33.7 (C3), 26.6 (C7/C8), 26.0 (C12/C13), 25.3 (C7/C8), 24.2 (C12/C13).

FTIR (ν_{max}, cm^{-1}): 3276 (w, NH and alkyne CH), 2992 (w), 2941 (w), 1450 (w), 1371 (m), 1320 (w), 1252 (m), 1205 (m), 1176 (s), 1068 (s), 995 (s), 980 (s), 912 (m), 885 (s), 865 (s), 845 (m), 802 (m), 756 (m).

HRMS (ESI): calculated for $C_{15}H_{24}NO_8S$ $[M+H]^+$ 378.1217, found 378.1216.

R_f = 0.36 (10% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -24.4 ($CHCl_3$, *c* = 1.0).



***tert*-Butyl (*S*)-(4-methyl-2-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)pentyl)carbamate:** Following the general procedure for propargylamide synthesis *via* EDC coupling in the presence of DIPEA using *N*-Boc-pregabalin (1.037 g, 4.0 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a white amorphous solid (0.617 g, 2.08 mmol, 52%), m.p. 81-83 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.92 (br s, 1 H, C3-NH), 4.82 (br s, 1 H, C7-NH), 4.09 – 3.99 (m, 2 H, H3), 3.23 (ddd, *J* = 14.1, 6.5, 3.9 Hz, 1 H, H7a), 3.01 (dt, *J* = 14.1, 6.5 Hz, 1 H, H7b), 2.21 (t, *J* = 2.5 Hz, 1 H, H1), 2.17 – 2.08 (m, 2 H, H5), 2.07 – 2.00 (m, 1 H, H6), 1.68

– 1.60 (m, 1 H, H12), 1.44 (s, 9 H, H10), 1.13 (t, *J* = 7.2 Hz, 2 H, H11), 0.93 – 0.85 (m, 6 H, H13 and H14).

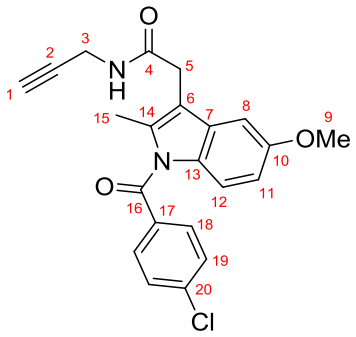
^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3 (br, C4), 157.1 (br, C8), 79.9 (br, C2), 79.7 (br, C9), 71.3 (br, C1), 43.5 (br, C7), 41.7 (br, C11), 39.2 (C5), 34.6 (br, C6), 29.3 (C3), 28.5 (C10), 25.3 (C12), 22.9 (C13/C14), 22.8 (C13/C14).

FTIR (ν_{max}, cm^{-1}): 3313 (m, NH and alkyne CH), 2958 (m), 2931 (m), 2870 (w), 1691 (s, C=O), 1647 (s, C=O), 1531 (s), 1452 (w), 1391 (w), 1366 (m), 1272 (m), 1251 (m), 1169 (s), 1023 (w), 856 (w).

HRMS (ESI): calculated for $C_{16}H_{28}N_2O_3Na$ $[M+Na]^+$ 319.1992, found 319.1980.

R_f = 0.34 (40% EtOAc/hexane).

$[\alpha]_D^{25.0}$ = -10.2 ($CHCl_3$, *c* = 1.0).



2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(prop-2-yn-1-yl)acetamide: Following the general procedure for propargylamide synthesis *via* EDC coupling using indomethacin (1.79 g, 5.0 mmol), purified by silica gel column chromatography (eluent: 50% EtOAc/hexane) provided the title compound as a pale-yellow amorphous solid (0.636 g, 1.61 mmol, 32%), m.p. 171-173 °C. (N.B. Product is highly insoluble and the reaction mixture was diluted/extracted with copious CH_2Cl_2).

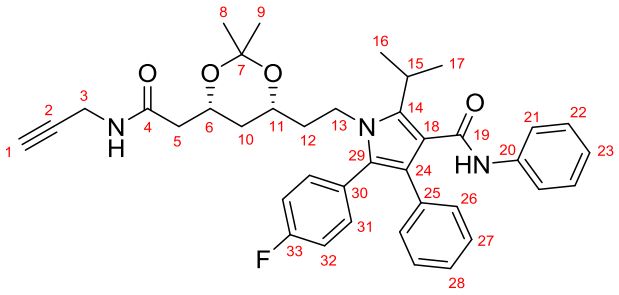
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.7 Hz, 2 H, H18), 7.49 (d, *J* = 8.7 Hz, 2 H, H19), 6.89 – 6.86 (m, 2 H, H8 and H12), 6.71 (dd, *J* = 9.0, 2.5 Hz, 1 H, H11), 5.77 (br s, 1 H, NH), 4.01 (dd, *J* = 5.5, 2.5 Hz, 2 H, H3), 3.83 (s, 3 H, H9), 3.67 (s, 2 H, H5), 2.39 (s, 3 H, H15), 2.16 (t, *J* = 2.5 Hz, 1 H, H1).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C4), 168.5 (C16), 156.5 (C10), 139.8 (C20), 136.6 (C14), 133.7 (C17), 131.4 (C18), 131.0 (C13), 130.3 (C7), 129.4 (C19), 115.3 (C12), 112.6 (C11), 112.4 (C6), 100.9 (C8), 79.5 (C2), 71.7 (C1), 55.9 (C9), 32.2 (C5), 29.4 (C3), 13.4 (C15).

FTIR (ν_{max}, cm^{-1}): 3297 (m, NH and alkyne CH), 2930 (w), 1679 (s, C=O), 1641 (s, C=O), 1596 (m), 1532 (m), 1477 (s), 1401 (w), 1355 (s), 1322 (s), 1290 (w), 1265 (w), 1222 (s), 1179 (w), 1150 (m), 1089 (m), 1069 (m), 1038 (w), 1012 (w), 992 (w), 927 (w), 868 (w), 835 (w), 801 (w), 755 (m).

HRMS (ESI): calculated for $C_{22}H_{20}N_2O_3Cl$ $[M+H]^+$ 395.1157, found 395.1169.

***R*$_f$** = 0.42 (5% EtOAc/hexane).



1-(2-((4*R*,6*R*)-2,2-Dimethyl-6-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide:

Atorvastatin calcium salt (0.994 g, 1.66 mmol with respect to one atorvastatin equivalent, 1 equiv.) was dissolved in 1 M HCl aqueous solution (25 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to provide the carboxylic acid. The residual foam was redissolved in acetone (8 mL) and 2,2-dimethoxypropane (2 mL), then (±)-camphorsulfonic acid (77.1 mg, 0.33 mmol, 0.2 equiv.) was added. The mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with Et_3N (0.05 mL) and evaporated under reduced pressure to provide crude acetonide-protected atorvastatin. Then, following the general procedure for propargylamide synthesis *via* EDC coupling in the presence of DIPEA using crude acetonide-protected atorvastatin, purified by silica gel column chromatography (eluent: 50% EtOAc/hexane) provided the title compound as a white foam (0.470 g, 0.74 mmol, 45% over three steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 – 7.13 (m, 9 H, H22, H26, H27, H28 and H31), 7.06 (d, *J* = 7.9 Hz, 2 H, H21), 7.02 – 6.96 (m, 3 H, H23 and H32), 6.86 (br s, 1 H, C19-NH), 6.40 (br t, *J* = 4.9 Hz, 1 H, C3-NH), 4.17 – 4.11 (m, 1 H, H6), 4.11 – 4.04 (m, 1 H, H13a), 4.04 – 4.00 (m, 2 H, H3), 3.86 – 3.79 (m, 1 H, H13b), 3.72 – 3.65 (m, 1 H, H11), 3.62 – 3.53 (m, 1 H, H15), 2.34 (dd, *J* = 15.1, 7.4 Hz, 1 H, H5a), 2.29 (dd, *J* = 15.1, 4.1 Hz, 1 H, H5b), 2.21 (t, *J* = 2.5 Hz, 1 H, H1), 1.71 – 1.61 (m, 2 H, H12), 1.53 (superimposed d, *J* = 7.1 Hz, 6 H, H16 and

H17), 1.38 (s, 3 H, H8/H9), 1.34 (s, 3 H, H8/H9), 1.31 (dt, *J* = 12.8, 2.3 Hz, 1 H, H10a), 1.09 (dt, *J* = 12.8, 11.7 Hz, 1 H, H10b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.1 (C4), 164.9 (C19), 162.4 (d, *J* = 247.8 Hz, C33), 141.6 (C14), 138.5 (C20), 134.7 (C25), 133.3 (d, *J* = 8.1 Hz, C31), 130.6 (C26), 128.9 (C29), 128.8 (C27), 128.5 (C22), 128.4 (d, *J* = 3.3 Hz, C30), 126.7 (C28), 123.7 (C23), 122.0 (C24), 119.7 (C21), 115.52 (d, *J* = 21.5 Hz, C32), 115.50 (C18), 99.1 (C7), 79.6 (C2), 71.6 (C1), 66.5 (C11), 66.2 (C6), 42.8 (C5), 40.9 (C13), 38.1 (C12), 35.8 (C10), 30.1 (C8/C9), 29.2 (C3), 26.2 (C15), 21.9 (C16/C17), 21.7 (C16/C17), 19.9 (C8/C9).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.6 (s, 1 F, F33).

FTIR (ν_{max}, cm^{-1}): 3302 (w, NH and alkyne CH), 3051 (w), 2960 (w), 1652 (m, C=O), 1595 (m), 1526 (s), 1508 (s), 1436 (m), 1381 (m), 1313 (m), 1265 (m), 1222 (m), 1201 (m), 1169 (m), 1156 (s), 1114 (w), 1094 (w), 1032 (w), 994 (w), 964 (w), 942 (w), 918 (w), 886 (w), 841 (w), 809 (w).

HRMS (ESI): calculated for $C_{39}H_{43}FN_3O_4$ $[M+H]^+$ 636.3232, found 636.3236.

$\boldsymbol{R_f}$ = 0.35 (50% EtOAc/hexane).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -4.3 ($CHCl_3$, *c* = 1.0).

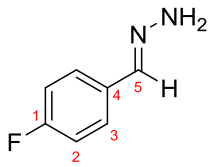
5.3.4. Synthetic procedures and characterisation for hydrazone starting materials

General procedure for aldehyde-derived hydrazone formation: General procedure is as described previously (Section 5.2.2).

(4-Chlorobenzylidene)hydrazine (62): Prepared as described previously (Section 5.2.2).

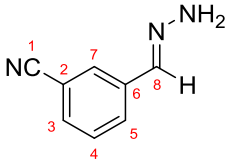
(4-Bromobenzylidene)hydrazine: Prepared as described previously (Section 5.2.2).

(3-Methoxybenzylidene)hydrazine: Prepared as described previously (Section 5.2.2).



(4-Fluorobenzylidene)hydrazine: Following the general procedure for aldehyde-derived hydrazone formation using 4-fluorobenzaldehyde (2.48 g, 20.0 mmol), provided the title compound as a colourless oil (2.75 g, 19.9 mmol, 99%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (s, 1 H, H5), 7.52 (dd, *J* = 8.7, 5.5 Hz, 2 H, H3), 7.04 (t, *J* = 8.7 Hz, 2 H, H4), 5.47 (br s, 2 H, NH).
^{13}C NMR (150 MHz, $CDCl_3$): δ 163.1 (d, *J* = 248.2 Hz, C1), 142.0 (C5), 131.5 (d, *J* = 3.2 Hz, C4), 127.9 (d, *J* = 8.2 Hz, C3), 115.7 (d, *J* = 21.9 Hz, C2).
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.6 (s, 1 F, F1).
FTIR (ν_{max}, cm^{-1}): 3379 (w, NH_2), 3192 (w, NH_2), 2905 (w), 1604 (m), 1508 (s), 1398 (w), 1300 (w), 1228 (s), 1154 (m), 1080 (w), 1012 (w), 947 (w), 919 (w), 875 (w), 832 (s), 797 (m).
HRMS (ESI): calculated for $C_7H_7FN_2Na$ $[M+Na]^+$ 161.0485, found 161.0484.



3-(Hydrazonomethyl)benzonitrile: Following the general procedure for aldehyde-derived hydrazone formation using 3-formylbenzonitrile (2.62 g, 20.0 mmol), provided the title

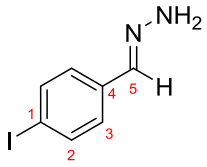
compound as a pale yellow amorphous solid (2.90 g, 19.9 mmol, 99%), m.p. 74-77 °C (lit. m.p.[184] 83-84°C). Data are consistent with a reported example.[184]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (t, *J* = 1.3 Hz, 1 H, H7), 7.74 (dt, *J* = 7.8 Hz, 1.3 Hz, 1 H, H5), 7.68 (s, 1 H, H8), 7.54 (dt, *J* = 7.8, 1.3 Hz, 1 H, H3), 7.43 (t, *J* = 7.8 Hz, 1 H, H4), 5.73 (br s, 2 H, NH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 139.6 (C8), 136.7 (C6), 131.6 (C3), 130.1 (C5), 129.55 (C7), 129.47 (C4), 118.8 (C1), 112.9 (C2).

FTIR (ν_{max}, cm^{-1}): 3402 (m, NH_2), 3292 (w, NH_2), 3215 (w), 2917 (w), 2231 (s, C≡N), 1590 (m), 1573 (m), 1481 (w), 1434 (w), 1388 (w), 1284 (w), 1245 (w), 1157 (w), 1088 (w), 918 (m), 798 (s).

HRMS (ESI): calculated for $C_8H_7N_3Na$ $[M+Na]^+$ 168.0532, found 168.0535.



(4-Iodobenzylidene)hydrazine: Following the general procedure for aldehyde-derived hydrazone formation using 4-iodobenzaldehyde (9.28 g, 40.0 mmol), provided the title compound as a pale yellow amorphous solid (9.82 g, 39.9 mmol, 99%), m.p. 96-98 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.4 Hz, 2 H, H2), 7.65 (s, 1 H, H5), 7.27 (d, *J* = 8.4 Hz, 2 H, H3), 5.57 (br s, 2 H, NH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.8 (C5), 137.8 (C2), 134.8 (C4), 127.9 (C3), 94.3 (C1).

FTIR (ν_{max}, cm^{-1}): 3360 (m, NH_2), 3196 (w, NH_2), 2912 (w), 1594 (w), 1483 (w), 1389 (m), 1080 (w), 1059 (w), 1004 (w), 925 (w), 912 (w), 863 (w), 818 (s).

HRMS (ESI): calculated for $C_7H_7N_2INa$ $[M+Na]^+$ 268.9546, found 268.9555.

5.3.5. Synthetic procedures and characterisation for asymmetric allenylation

Stock solution of 188-CuI: To a mixture of 2,6-bis((*S*)-4-(*tert*-butyl)-1-(4-(pentafluorosulfanyl)phenyl)-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (**188**) (0.549 g, 0.75 mmol) and copper(I) iodide (95.2 mg, 0.50 mmol) was added 1,4-dioxane (50 mL) and Et_3N (1.39 mL, 10.0 mmol). The mixture was stirred at r.t. for 2 h, resulting in a brown-red solution of the ligand/copper complex. The solution was stored at -20 °C under Ar as a precaution.

General procedure for racemic allenylation:

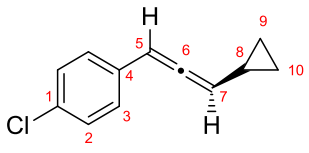
Conditioning phase: A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through a column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1} for 20 min and the reactor output was monitored using a FlowIR® device (SiComp head, 2100-2000 cm^{-1}). The flow was switched to solvent (DIPEA, 0.2 M in CH_2Cl_2) for 10 min. The column was then ready for the generation of the diazo compound.

Generation phase: A 5 mL microwave vial was charged with the appropriate alkyne (0.2 mmol, 1.0 equiv.), copper(I) iodide (3.9 mg, 0.02 mmol, 0.1 equiv.), 1,4-dioxane (2 mL) and Et_3N (0.05 mL, 0.4 mmol, 2 equiv.) and pre-mixed for 10 min. A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through the pre-conditioned column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak was stable, 3 mL of the output (1.5 equiv. with respect to the hydrazone) was directly added into the reaction vial (over 6 min) containing the copper acetylide and the reaction mixture further stirred at r.t. for 10 min. The mixture was then filtered through a pad of Celite, eluting with Et_2O, and the filtrate evaporated under reduced pressure. The residue was immediately purified by silica gel column chromatography to provide the desired disubstituted allene product. Any excess diazo compound produced during the conditioning phase or the generation phase before steady-state was reached was gently quenched by directing the output of the flow reactor into a stirred suspension of copper(I) iodide (0.10 g) in MeOH (25 mL).

General procedure for asymmetric allenylation:

Conditioning phase: A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through a column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1} for 20 min and the reactor output was monitored using a FlowIR® device (SiComp head, 2100-2000 cm^{-1}). The flow was switched to solvent (DIPEA, 0.2 M in CH_2Cl_2) for 10 min. The column was then ready for the generation of the diazo compound.

Generation phase: To a 5 mL microwave vial was added the appropriate alkyne (0.2 mmol, 1.0 equiv.), then an aliquot of the vigorously stirred **188**-CuI stock solution (2.05 mL, containing 0.15 equiv. ligand, 0.1 equiv. CuI and 2 equiv. Et_3N) was added. The mixture was pre-mixed at r.t. for 10 min, forming a clear red-orange homogeneous solution of the copper acetylide-ligand complex. A solution of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 was passed through the pre-conditioned column reactor (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak was stable, 4 mL of the output (2.0 equiv. with respect to the hydrazone) was directly added into the reaction vial (over 8 min) containing the copper acetylide-ligand complex and the reaction mixture further stirred at r.t. for 10 min. The solution was evaporated under reduced pressure and the residue taken up in Et_2O (5 mL). The mixture was then filtered through a pad of Celite, eluting with Et_2O, and the filtrate evaporated under reduced pressure. The residue was immediately purified by silica gel column chromatography to provide the desired allene (and alkyne) cross-products. Any excess diazo compound produced during the conditioning phase or the generation phase before steady-state was reached was gently quenched by directing the output of the flow reactor into a stirred suspension of copper(I) iodide (0.10 g) in MeOH (25 mL).



(*R*)-74

(*R*)-1-Chloro-4-(3-cyclopropylpropa-1,2-dien-1-yl)benzene ((*R*)-74): Following the general procedure for asymmetric allenylation using cyclopropylacetylene (**106**) (13.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (11.3 mg,

0.059 mmol, 30%, 87% *ee*). Data are consistent with racemic spectra as reported in Section 5.2.3.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 6.16 (d, *J* = 6.4 Hz, 1 H, H5), 5.45 (t, 1 H, *J* = 6.4 Hz, H7), 1.39 – 1.31 (m, 1 H, H8), 0.81 – 0.73 (m, 2 H, H9a and H10a), 0.50 – 0.39 (m, 2 H, H9b and H10b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.1 (C6), 133.6 (C4), 132.5 (C1), 128.8 (C2), 128.0 (C3), 100.1 (C7), 95.5 (C5), 9.5 (C8), 7.2 (C9/C10), 7.1 (C9/C10).

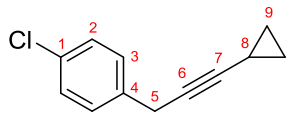
FTIR (ν_{max}, cm^{-1}): 3083 (w), 3005 (w), 2923 (w), 1948 (w, C=C=C), 1593 (w), 1573 (w), 1490 (s), 1457 (w), 1427 (w), 1397 (w), 1354 (w), 1296 (w), 1273 (w), 1251 (w), 1198 (w), 1174 (w), 1090 (s), 1047 (w), 1013 (m), 963 (w), 928 (w), 889 (w), 874 (m), 831 (s), 811 (s), 751 (m).

HRMS (ESI): calculated for $C_{12}H_{12}Cl$ $[M+H]^+$ 191.0622, found 191.0620.

R_f = 0.52 (hexane).

$[\alpha]_D^{25.0}$ = -183.9 ($CHCl_3$, *c* = 1.0, 87% *ee*).

HPLC: Chiralpak OD-H, hexane, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 6.7 (minor), 9.9 (major).



74'

1-Chloro-4-(3-cyclopropylprop-2-yn-1-yl)benzene (74′): Isolated as the alkyne cross-product from asymmetric allenylation of cyclopropylacetylene (**106**) and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as a colourless oil (26.7 mg, 0.140 mmol, 70%).

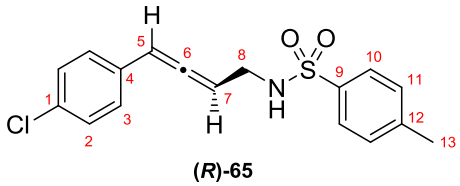
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 4 H, H2 and H3), 3.51 (d, *J* = 2.0 Hz, 2 H, H5), 1.33 – 1.16 (m, 1 H, H8), 0.78 – 0.72 (m, 2 H, H9a), 0.68 – 0.64 (m, 2 H, H9b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 136.1 (C4), 132.3 (C1), 129.3 (C3), 128.6 (C2), 86.2 (C7), 72.5 (C6), 24.7 (C5), 8.2 (C8), -0.3 (C9).

FTIR (ν_{max}, cm^{-1}): 3010 (w), 2921 (w), 2853 (w), 1703 (w), 1596 (w), 1578 (w), 1490 (s), 1421 (m), 1406 (m), 1360 (w), 1291 (w), 1202 (w), 1177 (w), 1088 (m), 1052 (w), 1035 (w), 1016 (s), 914 (w), 886 (m), 798 (s).

HRMS (ESI): calculated for $C_{12}H_{12}Cl$ $[M+H]^+$ 191.0622, found 191.0628.

$\boldsymbol{R_f}$ = 0.24 (hexane).



(*R*)-65

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide ((*R*)-65): Following the general procedure for asymmetric allenylation using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**60**) (41.8 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 1% Et_2O/CH_2Cl_2) provided the title compound as an off-white amorphous solid (33.7 mg, 0.101 mmol, 51%, 97% *ee*), m.p. 86-88 °C. Data are consistent with racemic spectra as reported in Section 5.2.3.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2 H, H10), 7.27 (d, *J* = 8.2 Hz, 2 H, H11), 7.24 (d, *J* = 8.4 Hz, 2 H, H2), 7.12 (d, *J* = 8.4 Hz, 2 H, H3), 6.17 (dt, *J* = 6.2, 3.0 Hz, 1 H, H5), 5.55 (q, *J* = 6.2 Hz, 1 H, H7), 4.68 (br s, 1 H, NH), 3.73 – 3.68 (m, 2 H, H8), 2.42 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.8 (C6), 143.8 (C12), 137.0 (C9), 133.3 (C1), 131.9 (C4), 129.9 (C11), 129.0 (C2), 128.2 (C3), 127.3 (C10), 97.1 (C5), 92.6 (C7), 41.7 (C8), 21.7 (C13).

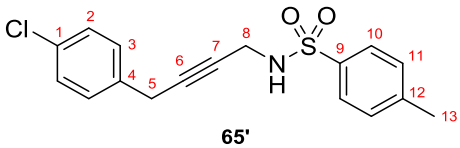
FTIR (ν_{max}, cm^{-1}): 3276 (w, NH), 2924 (w), 1957 (w, C=C=C), 1723 (w), 1597 (w), 1491 (m), 1408 (w), 1323 (m), 1265 (w), 1155 (s), 1090 (s), 1013 (m), 874 (m), 834 (m), 812 (s).

HRMS (ESI): calculated for $C_{17}H_{15}NO_2SCl$ $[M-H]^-$ 332.0518, found 332.0517.

$\boldsymbol{R_f}$ = 0.56 (1% Et_2O/CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -205.7 ($CHCl_3$, *c* = 1.0, 97% *ee*).

HPLC: Chiralpak AS, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 58.4 (minor), 75.5 (major).



65'

***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)-4-methylbenzenesulfonamide (65′):** Isolated as the alkyne cross-product from asymmetric allenylation of 4-methyl-*N*-(prop-2-yn-1-

yl)benzenesulfonamide (**60**) and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as an off-white amorphous solid (18.8 mg, 0.056 mmol, 28%), m.p. 81-83 °C.

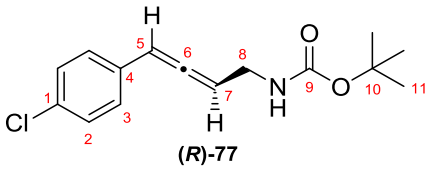
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2 H, H10), 7.26 – 7.22 (m, 4 H, H2 and H11), 7.07 (d, *J* = 8.4 Hz, 2 H, H3), 4.63 (br s, 1 H, NH), 3.88 (dt, *J* = 5.9, 2.2 Hz, 2 H, H8), 3.35 (t, *J* = 2.2 Hz, 2 H, H5), 2.38 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.8 (C12), 136.9 (C9), 134.6 (C4), 132.7 (C1), 129.7 (C11), 129.2 (C3), 128.7 (C2), 127.5 (C10), 82.5 (C6), 76.8 (C7), 33.5 (C8), 24.4 (C5), 21.7 (C13).

FTIR (ν_{max}, cm^{-1}): 3268 (w, NH), 3033 (w), 2925 (w), 1723 (w), 1597 (w), 1491 (m), 1408 (m), 1325 (m), 1306 (m), 1291 (m), 1215 (w), 1120 (w), 1186 (m), 1156 (s), 1090 (s), 1058 (m), 1015 (m), 812 (s), 751 (s).

HRMS (ESI): calculated for $C_{17}H_{16}NO_2SClNa$ $[M+Na]^+$ 356.0482, found 356.0486.

***R*$_f$** = 0.48 (1% Et_2O/CH_2Cl_2).



(*R*)-77

***tert*-Butyl (*R*)-(4-(4-chlorophenyl)buta-2,3-dien-1-yl)carbamate ((*R*)-77):** Following the general procedure for asymmetric allenylation using *N*-Boc-propargylamine (**239**) (31.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: CH_2Cl_2) provided the title compound as a pale yellow gum (27.6 mg, 0.099 mmol, 47%, 93% *ee*). Data are consistent with racemic spectra as reported in Section 5.2.3.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 6.24 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.65 (q, *J* = 6.4 Hz, 1 H, H7), 4.70 (br s, 1 H, NH), 3.92 – 3.75 (m, 2 H, H8), 1.40 (s, 9 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 155.8 (C9), 132.9 (C1), 132.7 (C4), 128.9 (C2), 128.2 (C3), 96.7 (C5), 94.1 (C7), 79.7 (C10), 39.1 (C8), 28.5 (C11).

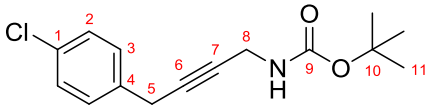
FTIR (ν_{max}, cm^{-1}): 3350 (w, NH), 2979 (w), 2929 (w), 1952 (w, C=C=C), 1693 (s, C=O), 1592 (w), 1491 (s), 1455 (m), 1392 (m), 1367 (m), 1249 (s), 1161 (s), 1091 (s), 1049 (w), 1014 (m), 952 (w), 858 (w), 834 (m), 781 (w), 760 (m).

HRMS (ESI): calculated for $C_{15}H_{18}NO_2ClNa$ $[M+Na]^+$ 302.0918, found 302.0909.

$\boldsymbol{R_f}$ = 0.42 (CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26.7}}$ = -101.0 ($CHCl_3$, *c* = 1.0, 93% *ee*).

HPLC: Chiralpak OD-H, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 7.7 (minor), 8.6 (major).



***tert*-Butyl (*R*)-(4-(4-chlorophenyl)buta-2,3-dien-1-yl)carbamate:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-Boc-propargylamine (**239**) and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as a colourless gum (19.8 mg, 0.071 mmol, 35%).

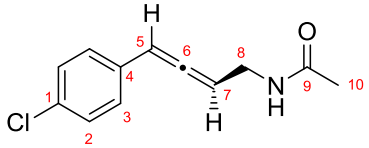
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.25 (d, *J* = 8.5 Hz, 2 H, H3), 4.70 (br s, 1 H, NH), 3.95 (br s, 2 H, H8), 3.55 (t, *J* = 2.1 Hz, 2 H, H5), 1.45 (s, 9 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.5 (C9), 135.2 (C4), 132.6 (C1), 129.4 (C3), 128.7 (C2), 80.6 (C6), 80.2 – 80.0 (br, C10), 78.9 (C7), 31.0 – 30.9 (br, C8), 28.5 (C11), 24.6 (C5).

FTIR (ν_{max}, cm^{-1}): 3338 (w, NH), 2978 (w), 2934 (w), 1692 (s, C=O), 1491 (s), 1455 (w), 1421 (w), 1408 (w), 1392 (w), 1366 (m), 1330 (w), 1275 (m), 1249 (m), 1163 (s), 1090 (m), 1048 (w), 1016 (m), 931 (w), 916 (w), 862 (w), 806 (w).

HRMS (ESI): calculated for $C_{15}H_{17}NO_2Cl$ $[M-H]^-$ 278.0953, found 278.0960.

$\boldsymbol{R_f}$ = 0.46 (CH_2Cl_2).



216

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)acetamide (216): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 50% Et_2O/CH_2Cl_2) provided the title compound as an off-white amorphous solid (20.8 mg, 0.094 mmol, 47%, 94% *ee*), m.p. 81-82 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H2), 7.20 (d, *J* = 8.6 Hz, 2 H, H3), 6.25 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.74 (br s, 1 H, NH), 5.67 (q, *J* = 6.4 Hz, 1 H, H7), 4.02 – 3.89 (m, 2 H, H8), 1.95 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.6 (C6), 170.1 (C9), 133.1 (C1), 132.4 (C4), 129.0 (C2), 128.1 (C3), 96.8 (C5), 93.5 (C7), 38.0 (C8), 23.3 (C10).

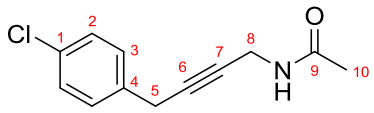
FTIR (ν_{max}, cm^{-1}): 3278 (m, NH), 3072 (w), 2928 (w), 1954 (w, C=C=C), 1651 (s, C=O), 1549 (s), 1491 (s), 1431 (m), 1390 (w), 1372 (m), 1344 (w), 1292 (m), 1234 (w), 1091 (m), 1042 (w), 1013 (m), 877 (w), 833 (m).

HRMS (ESI): calculated for $C_{12}H_{13}NOCl$ $[M+H]^+$ 222.0680, found 222.0676.

R_f = 0.32 (50% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.2}$ = -234.5 ($CHCl_3$, *c* = 1.0, 94% *ee*).

HPLC: ChiralART SA, 97:3 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 50.9 (minor), 54.1 (major).



***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and (4-chlorobenzylidene)-hydrazine (**62**), which provided the title compound as a white amorphous solid (14.1 mg, 0.064 mmol, 32%), m.p. 71-73 °C.

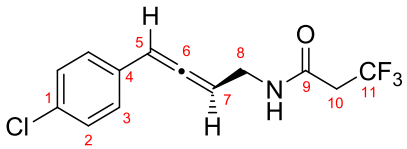
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.24 (d, *J* = 8.5 Hz, 2 H, H3), 5.71 (br s, 1 H, NH), 4.07 (dt, *J* = 4.9, 2.2 Hz, 2 H, H8), 3.55 (t, *J* = 2.2 Hz, 2 H, H5), 1.99 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C9), 135.0 (C4), 132.7 (C1), 129.4 (C3), 128.8 (C2), 81.0 (C6), 78.2 (C7), 29.9 (C8), 24.6 (C5), 23.2 (C10).

FTIR (ν_{max}, cm^{-1}): 3277 (m, NH), 3074 (w), 1651 (s, C=O), 1549 (m), 1492 (s), 1422 (m), 1373 (m), 1350 (m), 1289 (m), 1140 (w), 1090 (m), 1016 (m), 914 (w), 805 (w).

HRMS (ESI): calculated for $C_{12}H_{12}NOClNa$ $[M+Na]^+$ 244.0500, found 244.0496.

R_f = 0.34 (50% Et_2O/CH_2Cl_2).



217

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-3,3,3-trifluoropropanamide (217): Following the general procedure for asymmetric allenylation using 3,3,3-trifluoro-*N*-(prop-2-yn-1-yl)propanamide (33.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 25% EtOAc/hexane) provided the title compound as a yellow amorphous solid (29.9 mg, 0.103 mmol, 52%, 91% *ee*), m.p. 86-87 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 6.28 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 6.05 (br s, 1 H, NH), 5.67 (q, *J* = 6.4 Hz, 1 H, H7), 4.09 – 3.91 (m, 2 H, H8), 3.04 (q, *J* = 10.6 Hz, 2 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.5 (C6), 162.6 (q, *J* = 3.5 Hz, C9), 133.2 (C1), 132.1 (C4), 129.0 (C2), 128.2 (C3), 124.0 (q, *J* = 276.7 Hz, C11), 97.3 (C5), 92.8 (C7), 41.7 (q, *J* = 29.6 Hz, C10), 38.2 (C8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0 (s, 3 F, F11).

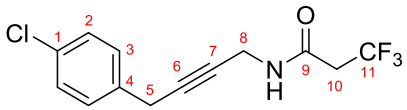
FTIR (ν_{max}, cm^{-1}): 3309 (m, NH), 2921 (w), 1953 (w, C=C=C), 1651 (s, C=O), 1556 (m), 1492 (m), 1390 (m), 1341 (w), 1264 (m), 1235 (m), 1141 (m), 1107 (m), 1093 (m), 1063 (w), 1014 (w), 920 (w), 880 (w), 851 (w), 836 (m), 752 (w).

HRMS (ESI): calculated for $C_{13}H_{10}F_3NOCl$ $[M-H]^-$ 288.0408, found 288.0407.

R_f = 0.23 (25% EtOAc/hexane).

$[\alpha]_D^{27.0}$ = -160.5 ($CHCl_3$, *c* = 1.0, 91% *ee*).

HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 15.2 (minor), 16.6 (major).



***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)-3,3,3-trifluoropropanamide:** Isolated as the alkyne cross-product from asymmetric allenylation of 3,3,3-trifluoro-*N*-(prop-2-yn-1-yl)propanamide and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as an off-white amorphous solid (14.8 mg, 0.051 mmol, 26%), m.p. 96-99 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.4 Hz, 2 H, H2), 7.23 (d, *J* = 8.4 Hz, 2 H, H3), 5.98 (br s, 1 H, NH), 4.12 (dt, *J* = 4.8, 2.3 Hz, 2 H, H8), 3.56 (t, *J* = 2.3 Hz, 2 H, H5), 3.08 (q, *J* = 10.5 Hz, 2 H, H10).

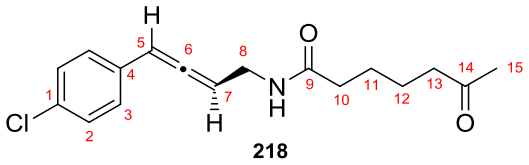
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2 (q, *J* = 3.6 Hz, C9), 134.8 (C4), 132.7 (C1), 129.3 (C3), 128.8 (C2), 124.0 (q, *J* = 276.7 Hz, C11), 81.8 (C6), 77.3 (C7), 41.7 (q, *J* = 29.8 Hz, C10), 30.3 (C8), 24.6 (C5).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9 (s, 3 F, F11).

FTIR (ν_{max}, cm^{-1}): 3304 (m, NH), 2970 (w), 2903 (w), 1651 (s, C=O), 1554 (m), 1492 (w), 1452 (w), 1424 (w), 1393 (m), 1351 (m), 1304 (w), 1264 (m), 1236 (m), 1129 (m), 1101 (m), 1092 (m), 1057 (m), 1016 (w), 927 (w), 854 (w), 841 (w), 796 (w), 760 (w).

HRMS (ESI): calculated for $C_{13}H_{11}F_3NOClNa$ $[M+Na]^+$ 312.0373, found 312.0375.

***R*$_f$** = 0.28 (25% EtOAc/hexane).



218

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-6-oxoheptanamide (218): Following the general procedure for asymmetric allenylation using 6-oxo-*N*-(prop-2-yn-1-yl)heptanamide (36.2 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 30% Et_2O/CH_2Cl_2) provided the title compound as a white crystalline solid (30.0 mg, 0.098 mmol, 49%, 96% *ee*), m.p. 94-95 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.20 (d, *J* = 8.5 Hz, 2 H, H3), 6.25 (dt, *J* = 6.5, 3.3 Hz, 1 H, H5), 5.85 (br s, 1 H, NH), 5.67 (q, *J* = 6.5 Hz, 1 H, H7), 4.05 – 3.99 (m, 1 H, H8a), 3.96 – 3.90 (m, 1 H, H8b), 2.39 – 2.34 (m, 2 H, H13), 2.18 – 2.14 (m, 2 H, H10), 2.10 (s, 3 H, H15), 1.56 – 1.49 (m, 4 H, H11 and H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 208.9 (C14), 204.6 (C6), 172.6 (C9), 133.0 (C1), 132.5 (C4), 128.9 (C2), 128.2 (C3), 96.9 (C5), 93.8 (C7), 43.3 (C13), 37.7 (C8), 36.4 (C10), 30.1 (C15), 25.1 (C11/C12), 23.2 (C11/C12).

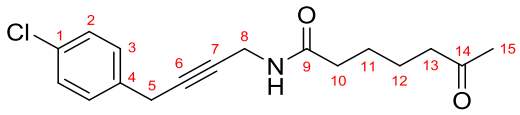
FTIR (ν_{max}, cm^{-1}): 3312 (m, NH), 3062 (w), 2943 (w), 1950 (w, C=C=C), 1708 (s, C=O), 1640 (s, C=O), 1538 (s), 1492 (s), 1461 (w), 1422 (w), 1361 (w), 1263 (w), 1236 (w), 1161 (w), 1092 (m), 1014 (w), 876 (w), 835 (m), 812 (w).

HRMS (ESI): calculated for $C_{17}H_{20}NO_2ClNa$ $[M+Na]^+$ 328.1075, found 328.1080.

R_f = 0.28 (30% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -210.9 ($CHCl_3$, *c* = 1.0, 96% *ee*).

HPLC: ChiralART SC, 85:15 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 33.8 (minor), 38.8 (major).



***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)-6-oxoheptanamide:** Isolated as the alkyne cross-product from asymmetric allenylation of 6-oxo-*N*-(prop-2-yn-1-yl)heptanamide and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as a white amorphous solid (23.3 mg, 0.076 mmol, 38%), m.p. 79-80 °C.

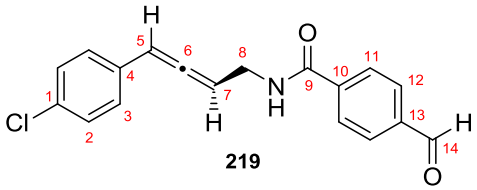
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2 H, H2), 7.23 (d, *J* = 8.6 Hz, 2 H, H3), 5.88 (br s, 1 H, NH), 4.07 (dt, *J* = 4.9, 2.2 Hz, 2 H, H8), 3.54 (t, *J* = 2.2 Hz, 2 H, H5), 2.44 (t, *J* = 6.8 Hz, 2 H, H13), 2.19 (t, *J* = 7.1 Hz, 2 H, H10), 2.12 (s, 3 H, H15), 1.65 – 1.54 (m, 4 H, H11 and H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.0 (C14), 172.3 (C9), 135.1 (C4), 132.6 (C1), 129.4 (C3), 128.7 (C2), 80.8 (C6), 78.3 (C7), 43.4 (C13), 36.2 (C10), 30.1 (C15), 29.7 (C8), 25.0 (C11/C12), 24.6 (C5), 23.2 (C11/C12).

FTIR (ν_{max}, cm^{-1}): 3287 (m, NH), 3056 (w), 2933 (w), 2866 (w), 1702 (s, C=O), 1635 (s, C=O), 1542 (m), 1492 (m), 1463 (w), 1419 (w), 1377 (w), 1360 (w), 1265 (w), 1237 (w), 1167 (w), 1097 (w), 1017 (w), 814 (w), 792 (w).

HRMS (ESI): calculated for $C_{17}H_{19}NO_2Cl$ $[M-H]^-$ 304.1110, found 304.1110.

R_f = 0.38 (30% Et_2O/CH_2Cl_2).



219

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-4-formylbenzamide (219): Following the general procedure for asymmetric allenylation using 4-formyl-*N*-(prop-2-yn-1-yl)benzamide (37.4 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column

chromatography (eluent: 5% Et_2O/CH_2Cl_2) provided the title compound as a pale yellow crystalline solid (29.2 mg, 0.094 mmol, 47%, 97% *ee*), m.p. 128-130 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 10.05 (s, 1 H, H14), 7.90 (d, *J* = 8.2 Hz, 2 H, H12), 7.83 (d, *J* = 8.2 Hz, 2 H, H11), 7.27 (d, *J* = 8.5 Hz, 2 H, H2), 7.22 (d, *J* = 8.5 Hz, 2 H, H3), 6.40 (br s, 1 H, NH), 6.30 (dt, *J* = 6.4, 3.3 Hz, 1 H, H5), 5.79 (q, *J* = 6.4 Hz, 1 H, H7), 4.26 – 4.13 (m, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.8 – 204.7 (br, C6), 191.6 (C14), 166.5 (C9), 139.6 (C10), 138.4 (C13), 133.3 (C1), 132.2 (C4), 130.0 (C12), 129.1 (C2), 128.2 (C3), 127.7 (C11), 97.3 (C5), 93.3 (C7), 38.4 (C8).

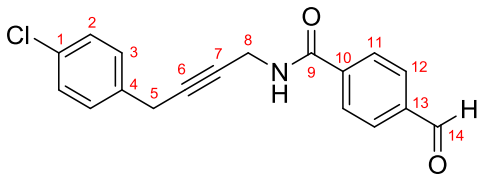
FTIR (ν_{max}, cm^{-1}): 3325 (w, NH), 3060 (w), 2838 (w), 1955 (w, C=C=C), 1705 (s, C=O), 1645 (s, C=O), 1610 (w), 1572 (w), 1537 (s), 1491 (s), 1430 (w), 1389 (w), 1346 (w), 1294 (m), 1207 (m), 1149 (w), 1090 (m), 1014 (w), 876 (w), 835 (m), 759 (w).

HRMS (ESI): calculated for $C_{18}H_{14}NO_2ClNa$ $[M+Na]^+$ 334.0605, found 334.0610.

R_f = 0.29 (5% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -473.6 ($CHCl_3$, *c* = 1.0, 97% *ee*).

HPLC: ChiralART SA, 93:7 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 43.3 (minor), 45.0 (major).



***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)-4-formylbenzamide:** Isolated as the alkyne cross-product from asymmetric allenylation of 4-formyl-*N*-(prop-2-yn-1-yl)benzamide and (4-chlorobenzylidene)hydrazine (**62**), after repurification by silica gel column chromatography (eluent: 40% EtOAc/hexane) of the alkyne-containing fractions, which provided the title compound as a white amorphous solid (20.8 mg, 0.067 mmol, 33%), m.p. 117-120 °C.

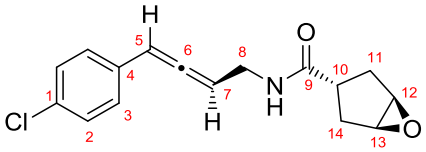
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.07 (s, 1 H, H14), 7.96 – 7.92 (m, 4 H, H11 and H12), 7.28 (d, *J* = 8.6 Hz, 2 H, H2), 7.25 (d, *J* = 8.6 Hz, 2 H, H3), 6.40 (br s, 1 H, NH), 4.31 (dt, *J* = 4.9, 2.2 Hz, 2 H, H8), 3.58 (t, *J* = 2.2 Hz, 2 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 191.6 (C14), 166.1 (C9), 139.1 (C10), 138.5 (C13), 134.9 (C4), 132.8 (C1), 130.0 (C12), 129.4 (C3), 128.8 (C2), 127.9 (C11), 81.7 (C6), 77.7 (C7), 30.6 (C8), 24.7 (C5).

FTIR (ν_{max}, cm^{-1}): 3312 (w, NH), 3064 (w), 2835 (w), 1704 (s, C=O), 1647 (s, C=O), 1610 (w), 1572 (w), 1538 (s), 1491 (s), 1419 (w), 1408 (w), 1386 (w), 1355 (w), 1291 (m), 1207 (m), 1154 (w), 1090 (m), 1016 (m), 977 (w), 848 (m), 801 (m), 757 (m).

HRMS (ESI): calculated for $C_{18}H_{13}NO_2Cl$ $[M-H]^-$ 310.0640, found 310.0639.

***R*$_f$** = 0.35 (5% Et_2O/CH_2Cl_2).



220

(1*R*,3*s*,5*S*)-*N*-((*R*)-4-(4-Chlorophenyl)buta-2,3-dien-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide (220): Following the general procedure for asymmetric allenylation using (1*R*,3*s*,5*S*)-*N*-(prop-2-yn-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide (33.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 30% Et_2O/CH_2Cl_2) provided the title compound as a white crystalline solid (32.0 mg, 0.110 mmol, 55%, 95% *ee*), m.p. 134-136 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2 H, H2), 7.18 (d, *J* = 8.5 Hz, 2 H, H3), 6.24 (dt, *J* = 6.6, 3.4 Hz, 1 H, H5), 5.75 (br s, 1 H, NH), 5.65 (q, *J* = 6.6 Hz, 1 H, H7), 4.04 – 3.98 (m, 1 H, H8a), 3.92 – 3.85 (m, 1 H, H8b), 3.49 – 3.44 (m, 2 H, H12 and H13), 2.32 (tt, *J* = 9.6, 7.8 Hz, 1 H, H10), 2.18 (dd, *J* = 13.9, 7.8 Hz, 1 H, H11a/H14a), 2.08 (dd, *J* = 14.0, 7.8 Hz, 1 H, H11a/H14a), 1.92 (ddd, *J* = 13.9, 9.6, 1.3 Hz, 1 H, H11b/H14b), 1.82 (ddd, *J* = 14.0, 9.6, 1.3 Hz, 1 H, H11b/H14b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.5 (C6), 173.9 (C9), 133.1 (C1), 132.3 (C4), 129.0 (C2), 128.1 (C3), 97.1 (C5), 93.7 (C7), 56.6 (C12 and C13), 39.0 (C10), 37.7 (C8), 31.93 (C11/C14), 31.86 (C11/C14).

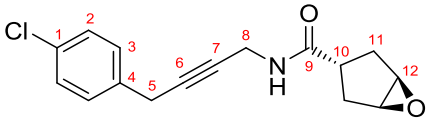
FTIR (ν_{max}, cm^{-1}): 3298 (m, NH), 3045 (w), 2925 (w), 1955 (w, C=C=C), 1649 (s, C=O), 1540 (m), 1491 (s), 1434 (w), 1391 (w), 1340 (w), 1294 (m), 1244 (w), 1220 (m), 1091 (m), 1060 (w), 1013 (w), 958 (w), 876 (w), 836 (s).

HRMS (ESI): calculated for $C_{16}H_{17}NO_2Cl$ $[M+H]^+$ 290.0942, found 290.0946.

***R*$_f$** = 0.37 (30% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -230.6 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SC, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 31.3 (minor), 36.1 (major).



(1*R*,3*s*,5*S*)-*N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide: Isolated as the alkyne cross-product from asymmetric allenylation of (1*R*,3*s*,5*S*)-*N*-(prop-2-yn-1-yl)-6-oxabicyclo[3.1.0]hexane-3-carboxamide and (4-chloro-benzylidene)hydrazine (**62**), which provided the title compound as a white amorphous solid (21.7 mg, 0.075 mmol, 37%), m.p. 131-132 °C.

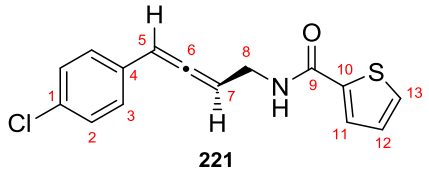
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.23 (d, *J* = 8.5 Hz, 2 H, H3), 5.76 (br s, 1 H, NH), 4.06 (dt, *J* = 5.0, 2.3 Hz, 2 H, H8), 3.54 (t, *J* = 2.3 Hz, 2 H, H5), 3.52 (s, 2 H, H12), 2.39 (tt, *J* = 9.6, 7.8 Hz, 1 H, H10), 2.24 (dd, *J* = 14.0, 7.8 Hz, 2 H, H11a), 1.95 (dd, *J* = 14.0, 9.6 Hz, 2 H, H11b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.7 (C9), 135.0 (C4), 132.7 (C1), 129.3 (C3), 128.8 (C2), 81.1 (C6), 78.1 (C7), 56.6 (C12), 38.9 (C10), 31.9 (C11), 30.0 (C8), 24.6 (C5).

FTIR (ν_{max}, cm^{-1}): 3283 (m, NH), 3031 (w), 2924 (w), 1649 (s, C=O), 1537 (s), 1491 (s), 1422 (w), 1408 (w), 1396 (w), 1348 (w), 1293 (m), 1243 (w), 1220 (m), 1090 (m), 1060 (w), 1016 (m), 958 (w), 838 (s), 807 (w).

HRMS (ESI): calculated for $C_{16}H_{16}NO_2ClNa$ $[M+Na]^+$ 312.0762, found 312.0770.

R_f = 0.46 (30% Et_2O/CH_2Cl_2).



221

(*R*)-*N*-(4-(4-Chlorophenyl)buta-2,3-dien-1-yl)thiophene-2-carboxamide (221): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)thiophene-2-carboxamide (33.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), stirred for 20 min after addition of diazo compound, purified by silica gel column chromatography

(eluent: CH_2Cl_2) provided the title compound as a yellow amorphous solid (30.7 mg, 0.106 mmol, 53%, 95% *ee*), m.p. 86-88 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.43 (m, 2 H, H11 and H13), 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 7.03 (dd, *J* = 4.9, 3.8 Hz, 1 H, H12), 6.28 (dt superimposed on br s, *J* = 6.0, 3.2 Hz, 2 H, H5 and NH), 5.76 (q, *J* = 6.0 Hz, 1 H, H7), 4.15 (td, *J* = 6.0, 3.2 Hz, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.8 (C6), 161.9 (C9), 138.7 (C10), 133.1 (C1), 132.3 (C4), 130.1 (C11), 129.0 (C2), 128.3 (C13), 128.2 (C3), 127.8 (C12), 97.0 (C5), 93.4 (C7), 38.3 (C8).

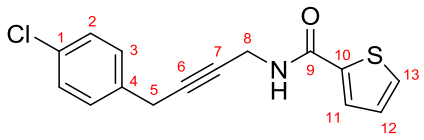
FTIR (ν_{max}, cm^{-1}): 3310 (w, NH), 3085 (w), 2921 (w), 1953 (w, C=C=C), 1626 (s, C=O), 1542 (s), 1510 (m), 1491 (s), 1420 (m), 1389 (w), 1358 (w), 1341 (w), 1297 (m), 1140 (w), 1090 (m), 1058 (w), 1013 (w), 875 (w), 859 (w), 833 (m).

HRMS (ESI): calculated for $C_{15}H_{12}NOSClNa$ $[M+Na]^+$ 312.0220, found 312.0226.

$\boldsymbol{R_f}$ = 0.34 (CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -290.4 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SC, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 30.6 (minor), 35.0 (major).



***N*-(4-(4-Chlorophenyl)but-2-yn-1-yl)thiophene-2-carboxamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)thiophene-2-carboxamide and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as a yellow gum (22.2 mg, 0.077 mmol, 38%).

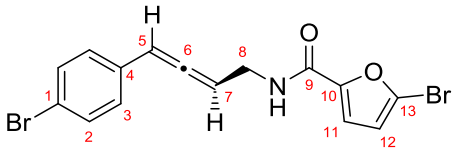
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 3.7, 1.1 Hz, 1 H, H11), 7.48 (dd, *J* = 5.0, 1.1 Hz, 1 H, H13), 7.28 (d, *J* = 8.6 Hz, 2 H, H2), 7.25 (d, *J* = 8.6 Hz, 2 H, H3), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1 H, H12), 6.17 (br s, 1 H, NH), 4.27 (dt, *J* = 5.3, 2.2 Hz, 2 H, H8), 3.57 (t, *J* = 2.2 Hz, 2 H, H5).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.6 (C9), 138.3 (C10), 135.0 (C4), 132.7 (C1), 130.4 (C13), 129.4 (C3), 128.8 (C2), 128.6 (C11), 127.8 (C12), 81.4 (C6), 78.0 (C7), 30.2 (C8), 24.7 (C5).

FTIR (ν_{max}, cm^{-1}): 3301 (w, NH), 3090 (w), 2924 (w), 1626 (s, C=O), 1539 (s), 1509 (m), 1490 (s), 1419 (m), 1360 (w), 1347 (w), 1291 (m), 1246 (w), 1151 (w), 1122 (w), 1089 (m), 1057 (w), 1035 (w), 1016 (w), 949 (w), 913 (w), 858 (w), 799 (m).

HRMS (ESI): calculated for $C_{15}H_{12}NOSClNa$ $[M+Na]^+$ 312.0220, found 312.0229.

R_f = 0.40 (CH_2Cl_2).



222

(*R*)-5-Bromo-*N*-(4-(4-bromophenyl)buta-2,3-dien-1-yl)furan-2-carboxamide (222): Following the general procedure for asymmetric allenylation using 5-bromo-*N*-(prop-2-yn-1-yl)furan-2-carboxamide (45.6 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 2% Et_2O/CH_2Cl_2) provided the title compound as an orange amorphous solid (42.3 mg, 0.107 mmol, 53%, 96% *ee*), m.p. 108-110 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.15 (d, *J* = 8.4 Hz, 2 H, H3), 7.04 (d, *J* = 3.5 Hz, 1 H, H11), 6.50 (br s, 1 H, NH), 6.41 (d, *J* = 3.5 Hz, 1 H, H12), 6.26 (dt, *J* = 6.1, 3.0 Hz, 1 H, H5), 5.71 (q, *J* = 6.1 Hz, 1 H, H7), 4.18 – 4.08 (m, 2 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.2 (C6), 157.2 (C9), 149.5 (C10), 132.8 (C4), 131.9 (C2), 128.6 (C3), 124.6 (C13), 121.2 (C1), 116.9 (C11), 114.3 (C12), 96.8 (C5), 93.1 (C7), 37.8 (C8).

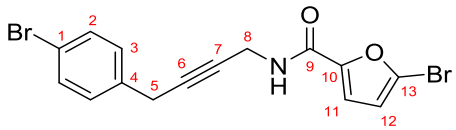
FTIR (ν_{max}, cm^{-1}): 3295 (w, NH), 1954 (w, C=C=C), 1647 (s, C=O), 1596 (m), 1575 (m), 1523 (s), 1488 (m), 1471 (s), 1430 (w), 1388 (w), 1342 (w), 1297 (m), 1221 (w), 1202 (w), 1171 (w), 1125 (w), 1070 (w), 1010 (m), 926 (w), 874 (w), 831 (m), 798 (m), 753 (w).

HRMS (ESI): calculated for $C_{15}H_{12}NO_2Br_2$ $[M+H]^+$ 395.9229, found 395.9234.

R_f = 0.37 (2% Et_2O/CH_2Cl_2).

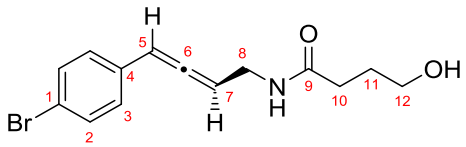
$[\alpha]_D^{25.0}$ = -238.4 ($CHCl_3$, *c* = 1.0, 96% *ee*).

HPLC: ChiralART SC, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 19.8 (minor), 21.8 (major).



5-Bromo-*N*-(4-(4-bromophenyl)but-2-yn-1-yl)furan-2-carboxamide: Isolated as the alkyne cross-product from asymmetric allenylation of 5-bromo-*N*-(prop-2-yn-1-yl)furan-2-carboxamide and (4-bromobenzylidene)hydrazine, which provided the title compound as an orange amorphous solid (31.0 mg, 0.078 mmol, 39%), m.p. 128-130 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2 H, H2), 7.20 (d, *J* = 8.4 Hz, 2 H, H3), 7.09 (d, *J* = 3.5 Hz, 1 H, H11), 6.44 (d superimposed on br s, *J* = 3.5 Hz, 2 H, H12 and NH), 4.25 (dt, *J* = 5.2, 2.3 Hz, 2 H, H8), 3.56 (t, *J* = 2.3 Hz, 2 H, H5).
^{13}C NMR (150 MHz, $CDCl_3$): δ 156.8 (C9), 149.2 (C10), 135.5 (C4), 131.8 (C2), 129.8 (C3), 124.8 (C13), 120.7 (C1), 117.1 (C11), 114.4 (C12), 81.3 (C6), 77.8 (C7), 29.5 (C8), 24.7 (C5).
FTIR (ν_{max}, cm^{-1}): 3286 (w, NH), 1650 (s, C=O), 1596 (m), 1574 (m), 1520 (s), 1487 (m), 1470 (s), 1419 (w), 1354 (w), 1295 (m), 1203 (w), 1172 (w), 1123 (w), 1071 (w), 1012 (m), 927 (w), 796 (m), 752 (w).
HRMS (ESI): calculated for $C_{15}H_{12}NO_2Br_2$ $[M+H]^+$ 395.9229, found 395.9230.
***R*$_f$** = 0.44 (2% Et_2O/CH_2Cl_2).



223

(*R*)-*N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)-4-hydroxybutanamide (223): Following the general procedure for asymmetric allenylation using 4-hydroxy-*N*-(prop-2-yn-1-yl)butanamide (28.2 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 20% THF/Et_2O) provided the title compound as a white amorphous solid (30.3 mg, 0.098 mmol, 49%, 91% *ee*), m.p. 89-91 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.3 Hz, 2 H, H2), 7.14 (d, *J* = 8.3 Hz, 2 H, H3), 6.24 (dt, *J* = 6.2, 3.0 Hz, 1 H, H5), 5.97 (br s, 1 H, NH), 5.65 (q, *J* = 6.2 Hz, 1 H, H7), 4.04 – 3.89 (m, 2 H, H8), 3.66 – 3.30 (m, 2 H, H12), 2.79 (br s, 1 H, OH), 2.34 – 2.29 (m, 2 H, H10), 1.84 – 1.79 (m, 2 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 173.5 (C9), 132.9 (C4), 131.9 (C2), 128.5 (C3), 121.2 (C1), 97.0 (C5), 93.6 (C7), 62.4 (C12), 37.9 (C8), 33.9 (C10), 28.1 (C11).

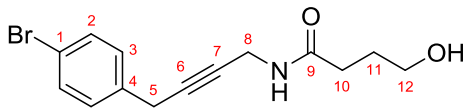
FTIR (ν_{max}, cm^{-1}): 3285 (br m, NH and OH), 2928 (w), 2876 (w), 1952 (w, C=C=C), 1637 (s, C=O), 1544 (m), 1488 (m), 1428 (w), 1380 (w), 1249 (w), 1217 (w), 1163 (w), 1070 (m), 1058 (m), 1010 (m), 918 (w), 881 (w), 832 (m), 810 (w).

HRMS (ESI): calculated for $C_{14}H_{16}NO_2BrNa$ $[M+Na]^+$ 332.0257, found 332.0262.

$\boldsymbol{R_f}$ = 0.20 (20% THF/Et_2O).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25.0}}$ = -237.5 ($CHCl_3$, *c* = 0.2, 91% *ee*).

HPLC: ChiralART SA, 93:7 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 16.7 (minor), 18.2 (major).



***N*-(4-(4-Bromophenyl)but-2-yn-1-yl)-4-hydroxybutanamide:** Isolated as the alkyne cross-product from asymmetric allenylation of 4-hydroxy-*N*-(prop-2-yn-1-yl)butanamide and (4-bromobenzylidene)hydrazine, which provided the title compound as a white amorphous solid (23.0 mg, 0.074 mmol, 37%), m.p. 73-74 °C.

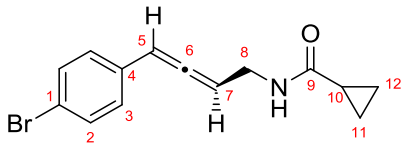
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 5.89 (br s, 1 H, NH), 4.08 (dt, *J* = 4.9, 2.3 Hz, 2 H, H8), 3.69 (t, *J* = 5.7 Hz, 2 H, H12), 3.53 (t, *J* = 2.3 Hz, 2 H, H5), 2.62 (br s, 1 H, OH), 2.36 (t, *J* = 6.5 Hz, 2 H, H10), 1.88 (tt, *J* = 6.5, 5.7 Hz, 2 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.1 (C9), 135.6 (C4), 131.8 (C2), 129.8 (C3), 120.7 (C1), 81.0 (C6), 78.2 (C7), 62.4 (C12), 33.7 (C10), 29.9 (C8), 28.0 (C11), 24.7 (C5).

FTIR (ν_{max}, cm^{-1}): 3272 (br m, NH and OH), 2937 (w), 1643 (s, C=O), 1542 (m), 1487 (s), 1420 (m), 1347 (w), 1259 (m), 1070 (m), 1012 (s), 916 (w), 801 (w).

HRMS (ESI): calculated for $C_{14}H_{16}NO_2BrNa$ $[M+Na]^+$ 332.0257, found 332.0268.

$\boldsymbol{R_f}$ = 0.26 (20% THF/Et_2O).



224

(*R*)-*N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)cyclopropanecarboxamide (224): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)cyclopropanecarboxamide (24.6 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 70% Et_2O/hexane) provided the title compound as an orange amorphous solid (30.0 mg, 0.103 mmol, 51%, 95% *ee*), m.p. 119-121 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.15 (d, *J* = 8.4 Hz, 2 H, H3), 6.24 (dt, *J* = 6.3, 3.1 Hz, 1 H, H5), 5.85 (br s, 1 H, NH), 5.67 (q, *J* = 6.3 Hz, 1 H, H7), 4.06 – 3.91 (m, 2 H, H8), 1.34 – 1.28 (m, 1 H, H10), 0.99 – 0.86 (m, 2 H, H11/H12), 0.74 – 0.64 (m, 2 H, H11/H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 – 204.6 (br, C6), 173.6 (C9), 133.0 (C4), 131.9 (C2), 128.5 (C3), 121.1 (C1), 96.8 (C5), 93.8 (C7), 38.0 (C8), 14.8 (C10), 7.37 (C11/C12), 7.36 (C11/C12).

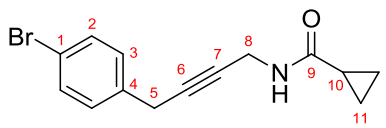
FTIR (ν_{max}, cm^{-1}): 3277 (m, NH), 3070 (w), 3011 (w), 2914 (w), 1954 (w, C=C=C), 1638 (s, C=O), 1545 (m), 1487 (m), 1451 (w), 1404 (w), 1336 (w), 1239 (m), 1196 (w), 1106 (w), 1070 (w), 1035 (w), 1010 (w), 991 (w), 912 (w), 879 (w), 830 (w).

HRMS (ESI): calculated for $C_{14}H_{14}NOBrNa$ $[M+Na]^+$ 314.0151, found 314.0136.

R_f = 0.29 (70% Et_2O/hexane).

$[\alpha]_D^{27.7}$ = -198.8 ($CHCl_3$, *c* = 0.5, 95% *ee*).

HPLC: ChiralART SA, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 20.1 (major), 28.3 (minor).



***N*-(4-(4-Bromophenyl)but-2-yn-1-yl)cyclopropanecarboxamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)cyclopropanecarboxamide and (4-bromobenzylidene)hydrazine, which provided the title compound as an orange amorphous solid (20.4 mg, 0.070 mmol, 35%), m.p. 135-136 °C.

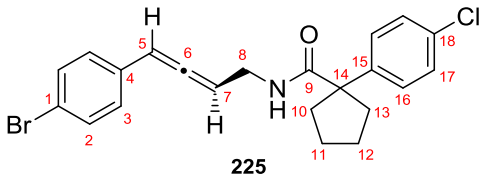
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 5.85 (br s, 1 H, NH), 4.10 (dt, *J* = 4.9, 2.3 Hz, 2 H, H8), 3.54 (t, *J* = 2.3 Hz, 2 H, H5), 1.37 – 1.32 (m, 1 H, H10), 1.00 – 0.96 (m, 2 H, H11a), 0.77 – 0.73 (m, 2 H, H11b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.3 (C9), 135.6 (C4), 131.7 (C2), 129.8 (C3), 120.7 (C1), 80.8 (C6), 78.6 (C7), 29.9 (C8), 24.7 (C5), 14.8 (C10), 7.5 (C11).

FTIR (ν_{max}, cm^{-1}): 3278 (m, NH), 3098 (w), 3010 (w), 2942 (w), 2859 (w), 1637 (s, C=O), 1589 (w), 1551 (s), 1486 (m), 1447 (w), 1426 (w), 1403 (m), 1335 (m), 1243 (m), 1230 (m), 1109 (w), 1074 (w), 1055 (w), 1034 (w), 1011 (m), 1002 (w), 937 (w), 908 (m), 840 (m), 823 (w), 806 (w), 788 (m), 770 (w).

HRMS (ESI): calculated for $C_{14}H_{14}NOBrNa$ $[M+Na]^+$ 314.0151, found 314.0160.

R_f = 0.36 (70% Et_2O/hexane).



225

(*R*)-*N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)-1-(4-chlorophenyl)cyclopentane-1-carboxamide (225): Following the general procedure for asymmetric allenylation using 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)cyclopentane-1-carboxamide (52.4 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a yellow gum (40.5 mg, 0.094 mmol, 47%, 95% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.15 (d, *J* = 8.7 Hz, 2 H, H17), 7.11 (d, *J* = 8.7 Hz, 2 H, H16), 7.05 (d, *J* = 8.4 Hz, 2 H, H3), 6.06 (dt, *J* = 6.3, 3.7 Hz, 1 H, H5), 5.58 (dt, *J* = 6.3, 4.8 Hz, 1 H, H7), 5.30 (br s, 1 H, NH), 3.95 – 3.85 (m, 1 H, H8a), 3.85 – 3.75 (m, 1 H, H8b), 2.44 – 2.33 (m, 2 H, H10/H13), 1.98 – 1.84 (m, 2 H, H10/H13), 1.84 – 1.71 (m, 2 H, H11/H12), 1.62 – 1.56 (m, 2 H, H11/H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.8 (C6), 175.9 (C9), 142.5 (C18), 132.9 (C4 and C15), 131.9 (C2), 128.8 (C16), 128.5 (C17), 128.4 (C3), 121.2 (C1), 97.5 (C5), 93.9 (C7), 58.9 (C14), 37.5 (C8), 37.1 (C10/C13), 37.0 (C10/C13), 24.01 (C11/C12), 24.00 (C11/C12).

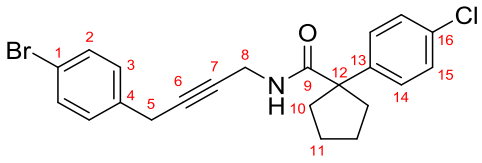
FTIR (ν_{max}, cm^{-1}): 3339 (w, NH), 2958 (w), 2873 (w), 1955 (w, C=C=C), 1646 (m, C=O), 1593 (w), 1488 (s), 1428 (w), 1401 (w), 1343 (w), 1262 (w), 1094 (m), 1070 (m), 1010 (s), 830 (s), 794 (m).

HRMS (ESI): calculated for $C_{22}H_{22}NOBrCl$ $[M+H]^+$ 430.0568, found 430.0550.

$\boldsymbol{R_f}$ = 0.33 (25% EtOAc/hexane).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -216.0 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 19.1 (minor), 19.9 (major).



***N*-(4-(4-Bromophenyl)but-2-yn-1-yl)-1-(4-chlorophenyl)cyclopentane-1-carboxamide:** Isolated as the alkyne cross-product from asymmetric allenylation of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)cyclopentane-1-carboxamide and (4-bromobenzylidene)-hydrazine, which provided the title compound as a white crystalline solid (25.1 mg, 0.058 mmol, 29%), m.p. 116-119 °C.

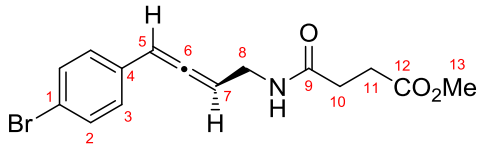
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.29 (d, *J* = 8.9 Hz, 2 H, H15), 7.27 (d, *J* = 8.9 Hz, 2 H, H14), 7.12 (d, *J* = 8.4 Hz, 2 H, H3), 5.29 (br s, 1 H, NH), 3.96 (dt, *J* = 5.3, 2.3 Hz, 2 H, H8), 3.48 (t, *J* = 2.3 Hz, 2 H, H5), 2.48 – 2.41 (m, 2 H, H10a), 2.00 – 1.93 (m, 2 H, H10b), 1.85 – 1.77 (m, 2 H, H11a), 1.70 – 1.64 (m, 2 H, H11b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 175.6 (C9), 142.5 (C13), 135.6 (C4), 133.0 (C16), 131.7 (C2), 129.7 (C3), 129.0 (C15), 128.4 (C14), 120.6 (C1), 80.7 (C6), 78.3 (C7), 58.9 (C12), 37.0 (C10), 30.2 (C8), 24.7 (C5), 24.0 (C11).

FTIR (ν_{max}, cm^{-1}): 3339 (w, NH), 2954 (w), 2874 (w), 1646 (m, C=O), 1593 (w), 1487 (s), 1454 (w), 1419 (w), 1401 (w), 1349 (w), 1327 (w), 1268 (m), 1184 (w), 1135 (w), 1093 (m), 1071 (m), 1012 (s), 963 (w), 907 (m), 825 (m), 799 (m), 762 (w).

HRMS (ESI): calculated for $C_{22}H_{22}NOBrCl$ $[M+H]^+$ 430.0568, found 430.0565.

$\boldsymbol{R_f}$ = 0.42 (25% EtOAc/hexane).

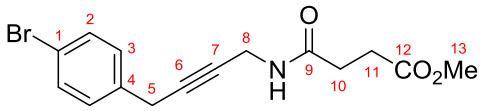


226

Methyl (*R*)-4-((4-(4-bromophenyl)buta-2,3-dien-1-yl)amino)-4-oxobutanoate (226): Following the general procedure for asymmetric allenylation using methyl 4-oxo-4-(prop-2-yn-1-ylamino)butanoate (33.8 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified

by silica gel column chromatography (eluent: 5% Et_2O/CH_2Cl_2) provided the title compound as an orange amorphous solid (29.4 mg, 0.087 mmol, 43%, 91% *ee*), m.p. 90-92 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 6.23 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.90 (br s, 1 H, NH), 5.65 (q, *J* = 6.4 Hz, 1 H, H7), 4.04 – 3.89 (m, 2 H, H8), 3.64 (s, 3 H, H13), 2.65 – 2.58 (m, 2 H, H11), 2.48 – 2.42 (m, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 173.6 (C12), 171.4 (C9), 132.9 (C4), 131.9 (C2), 128.5 (C3), 121.1 (C1), 96.9 (C5), 93.6 (C7), 52.0 (C13), 37.9 (C8), 31.1 (C10), 29.4 (C11).
FTIR (ν_{max}, cm^{-1}): 3305 (w, NH), 2922 (w), 2851 (w), 1951 (w, C=C=C), 1734 (s, C=O), 1648 (s, C=O), 1538 (m), 1488 (s), 1436 (m), 1362 (m), 1199 (m), 1166 (s), 1069 (m), 1028 (w), 1009 (s), 913 (w), 876 (m), 830 (m).
HRMS (ESI): calculated for $C_{15}H_{16}NO_3BrNa$ $[M+Na]^+$ 360.0206, found 360.0195.
R_f = 0.15 (5% Et_2O/CH_2Cl_2).
$[\alpha]_D^{28.0}$ = -157.9 ($CHCl_3$, *c* = 1.0, 91% *ee*).
HPLC: ChiralART SA, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 23.1 (minor), 26.3 (major).

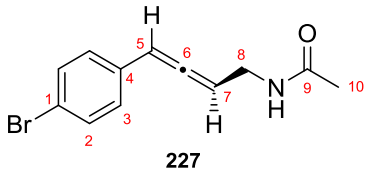


Methyl 4-((4-(4-bromophenyl)but-2-yn-1-yl)amino)-4-oxobutanoate: Isolated as the alkyne cross-product from asymmetric allenylation of methyl 4-oxo-4-(prop-2-yn-1-ylamino)butanoate and (4-bromobenzylidene)hydrazine, which provided the title compound as an off-white amorphous solid (25.2 mg, 0.075 mmol, 37%), m.p. 75-76 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 5.87 (br s, 1 H, NH), 4.08 (dt, *J* = 4.9, 2.2 Hz, 2 H, H8), 3.68 (s, 3 H, H13), 3.53 (t, *J* = 2.2 Hz, 2 H, H5), 2.68 (t, *J* = 6.8 Hz, 2 H, H11), 2.49 (t, *J* = 6.8 Hz, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5 (C12), 171.1 (C9), 135.6 (C4), 131.7 (C2), 129.8 (C3), 120.7 (C1), 80.9 (C6), 78.2 (C7), 52.0 (C13), 30.9 (C10), 29.9 (C8), 29.3 (C11), 24.7 (C5).
FTIR (ν_{max}, cm^{-1}): 3292 (w, NH), 3061 (w), 2950 (w), 2925 (w), 1735 (s, C=O), 1649 (s, C=O), 1535 (m), 1487 (s), 1437 (m), 1420 (m), 1363 (m), 1200 (m), 1168 (s), 1071 (m), 1012 (s), 915 (w), 845 (m), 802 (m).

HRMS (ESI): calculated for $C_{15}H_{16}NO_3BrNa$ $[M+Na]^+$ 360.0206, found 360.0200.

$\boldsymbol{R_f}$ = 0.20 (5% Et_2O/CH_2Cl_2).



227

(*R*)-*N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)acetamide (227): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 2% Et_2O/CH_2Cl_2) provided the title compound as an off-white amorphous solid (27.4 mg, 0.103 mmol, 51%, 96% *ee*), m.p. 92-94 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 6.24 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.70 (br s, 1 H, NH), 5.66 (q, *J* = 6.4 Hz, 1 H, H7), 4.03 – 3.89 (m, 2 H, H8), 1.95 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 – 204.6 (br, C6), 170.1 (C9), 132.9 (C4), 131.9 (C2), 128.5 (C3), 121.1 (C1), 96.9 (C5), 93.6 (C7), 37.9 (C8), 23.3 (10).

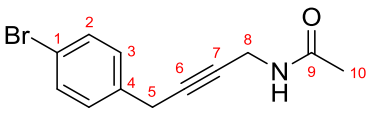
FTIR (ν_{max}, cm^{-1}): 3275 (m, NH), 3079 (w), 2930 (w), 1954 (w, C=C=C), 1651 (s, C=O), 1548 (s), 1488 (s), 1429 (m), 1372 (m), 1343 (w), 1291 (m), 1099 (w), 1070 (m), 1010 (m), 877 (w), 830 (m).

HRMS (ESI): calculated for $C_{12}H_{12}NOBrNa$ $[M+Na]^+$ 287.9994, found 287.9986.

$\boldsymbol{R_f}$ = 0.33 (50% Et_2O/CH_2Cl_2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -233.0 ($CHCl_3$, *c* = 1.0, 96% *ee*).

HPLC: ChiralART SA, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 24.2 (minor), 25.5 (major).



***N*-(4-(4-Bromophenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and (4-bromobenzylidene)hydrazine, which provided the title compound as an off-white amorphous solid (20.0 mg, 0.075 mmol, 38%), m.p. 82-84 °C.

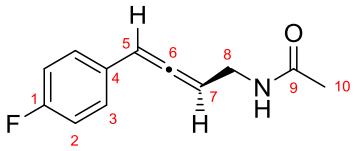
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 5.67 (br s, 1 H, NH), 4.07 (dt, *J* = 4.9, 2.2 Hz, 2 H, H8), 3.53 (t, *J* = 2.2 Hz, 2 H, H5), 1.99 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C9), 135.6 (C4), 131.7 (C2), 129.8 (C3), 120.7 (C1), 80.9 (C6), 78.3 (C7), 29.9 (C8), 24.7 (C5), 23.2 (C10).

FTIR (ν_{max}, cm^{-1}): 3273 (m, NH), 3079 (w), 1652 (s, C=O), 1548 (m), 1487 (s), 1421 (m), 1373 (m), 1350 (m), 1288 (m), 1184 (w), 1141 (w), 1070 (m), 1027 (w), 1012 (m), 914 (w), 801 (w).

HRMS (ESI): calculated for $C_{12}H_{12}NOBrNa$ $[M+Na]^+$ 287.9994, found 287.9985.

R_f = 0.39 (50% Et_2O/CH_2Cl_2).



228

(*R*)-*N*-(4-(4-Fluorophenyl)buta-2,3-dien-1-yl)acetamide (228): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and (4-fluorobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 50% Et_2O/CH_2Cl_2) provided the title compound as an off-white amorphous solid (18.3 mg, 0.089 mmol, 45%, 91% *ee*), m.p. 75-78 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.7, 5.4 Hz, 2 H, H3), 7.00 (t, *J* = 8.7 Hz, 2 H, H2), 6.27 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.66 (q, *J* = 6.4 Hz, 1 H, H7), 4.05 – 3.87 (m, 2 H, H8), 1.96 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.3 (C6), 170.1 (C9), 162.2 (d, *J* = 246.7 Hz, C1), 129.8 (d, *J* = 3.3 Hz, C4), 128.4 (d, *J* = 8.0 Hz, C3), 115.8 (d, *J* = 21.8 Hz, C2), 96.8 (C5), 93.3 (C7), 38.0 (C8), 23.4 (C10).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.7 (s, 1 F, F1).

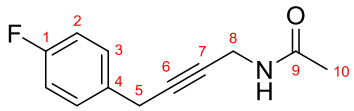
FTIR (ν_{max}, cm^{-1}): 3277 (w, NH), 3074 (w), 2925 (w), 1953 (w, C=C=C), 1651 (m, C=O), 1603 (w), 1548 (m), 1507 (s), 1432 (w), 1394 (w), 1373 (m), 1345 (w), 1285 (m), 1223 (s), 1156 (m), 1096 (w), 1041 (w), 1014 (w), 877 (w), 837 (m), 765 (w).

HRMS (ESI): calculated for $C_{12}H_{12}FNONa$ $[M+Na]^+$ 228.0795, found 228.0802.

R_f = 0.35 (50% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -201.5 ($CHCl_3$, *c* = 1.0, 91% *ee*).

HPLC: ChiralART SA, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 22.0 (minor), 22.9 (major).



***N*-(4-(4-Fluorophenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and (4-fluorobenzylidene)hydrazine, which provided the title compound as a white amorphous solid (14.2 mg, 0.069 mmol, 35%), m.p. 56-57 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.7, 5.4 Hz, 2 H, H3), 7.00 (t, *J* = 8.7 Hz, 2 H, H2), 5.67 (br s, 1 H, NH), 4.08 (dt, *J* = 4.8, 2.2 Hz, 2 H, H8), 3.55 (t, *J* = 2.2 Hz, 2 H, H5), 1.99 (s, 3 H, H10).

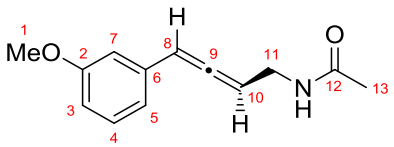
^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C9), 161.9 (d, *J* = 244.7 Hz, C1), 132.2 (d, *J* = 3.2 Hz, C4), 129.5 (d, *J* = 8.0 Hz, C3), 115.5 (d, *J* = 21.5 Hz, C2), 81.4 (C6), 78.0 (C7), 29.9 (C8), 24.4 (C5), 23.2 (C10).

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.4 (s, 1 F, F1).

FTIR (ν_{max}, cm^{-1}): 3278 (w, NH), 3073 (w), 2925 (w), 1651 (m, C=O), 1604 (w), 1548 (m), 1508 (s), 1424 (w), 1374 (w), 1350 (w), 1287 (w), 1221 (m), 1158 (w), 1094 (w), 1017 (w), 912 (w), 820 (w), 758 (w).

HRMS (ESI): calculated for $C_{12}H_{13}FNO$ $[M+H]^+$ 206.0976, found 206.0976.

***R*$_f$** = 0.42 (50% Et_2O/CH_2Cl_2).



229

(*R*)-*N*-(4-(3-Methoxyphenyl)buta-2,3-dien-1-yl)acetamide (229): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and (3-methoxybenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 40% Et_2O/CH_2Cl_2) provided the title compound as a colourless gum (19.4 mg, 0.089 mmol, 45%, 95% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.9 Hz, 1 H, H4), 6.87 (d, *J* = 7.9 Hz, 1 H, H5), 6.84 – 6.82 (m, 1 H, H7), 6.77 (dd, *J* = 7.9, 2.5 Hz, 1 H, H3), 6.27 (dt, *J* = 6.5, 3.3 Hz, 1 H, H8), 5.70 (br s, 1 H, NH), 5.67 (q, *J* = 6.5 Hz, 1 H, H10), 4.02 – 3.91 (m, 2 H, H11), 3.81 (s, 3 H, H1), 1.96 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.6 (C9), 170.1 (C12), 160.1 (C2), 135.3 (C6), 129.8 (C4), 119.6 (C5), 113.2 (C3), 112.2 (C7), 97.7 (C8), 93.1 (C10), 55.4 (C1), 38.0 (C11), 23.4 (C13).

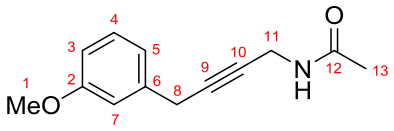
FTIR (ν_{max}, cm^{-1}): 3289 (m, NH), 3068 (w), 2938 (w), 2835 (w), 1951 (w, C=C=C), 1652 (s, C=O), 1598 (m), 1582 (m), 1549 (m), 1490 (m), 1467 (m), 1439 (m), 1408 (w), 1372 (w), 1344 (w), 1264 (m), 1155 (m), 1092 (w), 1043 (m), 995 (w), 883 (w), 787 (m).

HRMS (ESI): calculated for $C_{13}H_{15}NO_2Na$ $[M+Na]^+$ 240.0995, found 240.1000.

R_f = 0.31 (40% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -218.1 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SC, 85:15 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 16.3 (minor), 21.1 (major).



***N*-(4-(3-Methoxyphenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and (3-methoxybenzylidene)hydrazine, which provided the title compound as a colourless gum (15.9 mg, 0.073 mmol, 37%).

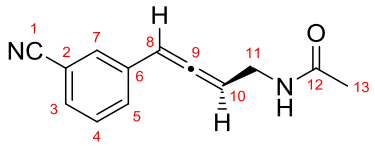
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (t, *J* = 8.0 Hz, 1 H, H4), 6.91 – 6.86 (m, 2 H, H5 and H7), 6.78 (dd, *J* = 8.0, 2.3 Hz, 1 H, H3), 5.69 (br s, 1 H, NH), 4.07 (dt, *J* = 4.8, 2.2 Hz, 2 H, H11), 3.81 (s, 3 H, H1), 3.56 (t, *J* = 2.2 Hz, 2 H, H8), 1.99 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C12), 159.9 (C2), 138.1 (C6), 129.7 (C4), 120.4 (C5), 113.9 (C3), 112.1 (C7), 81.5 (C9), 77.8 (C10), 55.4 (C1), 30.0 (C11), 25.2 (C8), 23.2 (C13).

FTIR (ν_{max}, cm^{-1}): 3283 (m, NH), 3070 (w), 2837 (w), 1651 (s, C=O), 1601 (m), 1586 (m), 1546 (m), 1489 (m), 1455 (m), 1436 (m), 1373 (w), 1351 (w), 1317 (w), 1283 (m), 1260 (s), 1155 (m), 1136 (w), 1090 (w), 1047 (m), 852 (w), 775 (m).

HRMS (ESI): calculated for $C_{13}H_{15}NO_2Na$ $[M+Na]^+$ 240.0995, found 240.1000.

R_f = 0.38 (40% Et_2O/CH_2Cl_2).



230

(*R*)-*N*-(4-(3-Cyanophenyl)buta-2,3-dien-1-yl)acetamide (230): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and 3-(hydrazonomethyl)benzonitrile, purified by silica gel column chromatography (eluent: 50% Et_2O/CH_2Cl_2) provided the title compound as a colourless gum (17.0 mg, 0.080 mmol, 40%, 89% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55 (s, 1 H, H7), 7.52 – 7.47 (m, 2 H, H3 and H5), 7.41 (t, *J* = 7.8 Hz, 1 H, H4), 6.27 (dt, *J* = 6.3, 3.1 Hz, 1 H, H8), 5.74 (q superimposed on br s, *J* = 6.3 Hz, 2 H, H10 and NH), 4.07 – 3.92 (m, 2 H, H11), 1.98 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.3 (C9), 170.2 (C12), 135.6 (C6), 131.1 (C5), 130.7 (C3), 130.3 (C7), 129.6 (C4), 118.8 (C1), 113.0 (C2), 96.1 (C8), 94.2 (C10), 38.0 (C11), 23.3 (C13).

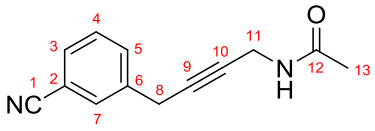
FTIR (ν_{max}, cm^{-1}): 3281 (m, NH), 3072 (w), 2929 (w), 2231 (m, C≡N), 1954 (w, C=C=C), 1651 (s, C=O), 1599 (w), 1543 (s), 1483 (m), 1432 (m), 1372 (m), 1344 (w), 1283 (m), 1228 (w), 1096 (w), 1043 (w), 999 (w), 898 (w), 801 (m).

HRMS (ESI): calculated for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1022, found 213.1017.

R_f = 0.25 (50% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -194.4 ($CHCl_3$, *c* = 1.0, 89% *ee*).

HPLC: ChiralART SA, 93:7 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 30.5 (minor), 32.8 (major).



***N*-(4-(3-Cyanophenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and 3-(hydrazonomethyl)-benzonitrile, which provided the title compound as a yellow amorphous solid (23.4 mg, 0.110 mmol, 55%), m.p. 87-90 °C.

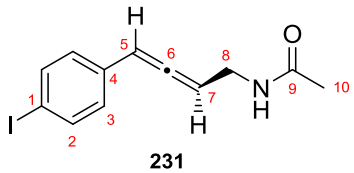
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1 H, H7), 7.56 – 7.51 (m, 2 H, H3 and H5), 7.41 (t, *J* = 7.8 Hz, 1 H, H4), 5.88 (br s, 1 H, NH), 4.08 (dt, *J* = 5.3, 2.2 Hz, 2 H, H11), 3.62 (t, *J* = 2.2 Hz, 2 H, H8), 2.00 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9 (C12), 138.1 (C6), 132.6 (C5), 131.5 (C7), 130.6 (C3), 129.4 (C4), 118.8 (C1), 112.7 (C2), 79.6 (C9), 79.2 (C10), 29.7 (C11), 24.8 (C8), 23.2 (C13).

FTIR (ν_{max}, cm^{-1}): 3290 (m, NH), 3065 (w), 2923 (w), 2231 (m, C≡N), 1652 (s, C=O), 1543 (s), 1483 (m), 1432 (m), 1374 (m), 1351 (w), 1285 (m), 1093 (w), 1027 (w), 788 (m).

HRMS (ESI): calculated for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1022, found 213.1028.

***R*$_f$** = 0.32 (50% Et_2O/CH_2Cl_2).



231

(*R*)-*N*-(4-(4-Iodophenyl)buta-2,3-dien-1-yl)acetamide (231): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)acetamide (19.4 mg, 0.2 mmol) and (4-iodobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 50% Et_2O/CH_2Cl_2) provided the title compound as an off-white amorphous solid (27.6 mg, 0.088 mmol, 44%, 95% *ee*), m.p. 118-119 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2 H, H2), 7.01 (d, *J* = 8.3 Hz, 2 H, H3), 6.22 (dt, *J* = 6.3, 3.2 Hz, 1 H, H5), 5.70 (br s, 1 H, NH), 5.66 (q, *J* = 6.3 Hz, 1 H, H7), 4.03 – 3.87 (m, 2 H, H8), 1.95 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 – 204.6 (br, C6), 170.1 (C9), 137.9 (C2), 133.5 (C4), 128.7 (C3), 97.0 (C5), 93.6 (C7), 92.5 (C1), 37.9 (C8), 23.3 (C10).

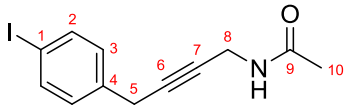
FTIR (ν_{max}, cm^{-1}): 3280 (m, NH), 3068 (w), 2925 (w), 1951 (w, C=C=C), 1651 (s, C=O), 1551 (s), 1484 (s), 1429 (w), 1372 (m), 1343 (w), 1291 (m), 1108 (w), 1058 (w), 1006 (m), 876 (w), 826 (m).

HRMS (ESI): calculated for $C_{12}H_{12}NOINa$ $[M+Na]^+$ 335.9856, found 335.9862.

***R*$_f$** = 0.38 (50% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -198.4 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SA, 97:3 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 58.0 (minor), 62.4 (major).



***N*-(4-(4-Iodophenyl)but-2-yn-1-yl)acetamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)acetamide and (4-iodobenzylidene)hydrazine, which provided the title compound as a yellow amorphous solid (22.4 mg, 0.072 mmol, 36%), m.p. 103-104 °C.

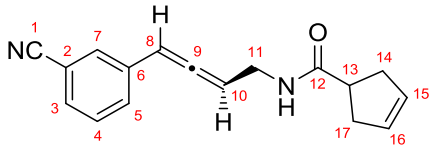
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2 H, H2), 7.06 (d, *J* = 8.3 Hz, 2 H, H3), 5.72 (br s, 1 H, NH), 4.07 (dt, *J* = 5.2, 2.1 Hz, 2 H, H8), 3.52 (t, *J* = 2.1 Hz, 2 H, H5), 1.99 (s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (C9), 137.7 (C2), 136.3 (C4), 130.1 (C3), 92.0 (C1), 80.8 (C6), 78.3 (C7), 29.9 (C8), 24.8 (C5), 23.2 (C10).

FTIR (ν_{max}, cm^{-1}): 3283 (m, NH), 3069 (w), 2919 (w), 1648 (s, C=O), 1544 (s), 1483 (s), 1420 (m), 1400 (m), 1373 (m), 1350 (m), 1287 (m), 1187 (w), 1140 (w), 1110 (w), 1087 (w), 1060 (w), 1027 (w), 1008 (s), 918 (w), 778 (m).

HRMS (ESI): calculated for $C_{12}H_{13}NOI$ $[M+H]^+$ 314.0036, found 314.0049.

***R*$_f$** = 0.45 (50% Et_2O/CH_2Cl_2).



232

(*R*)-*N*-(4-(3-Cyanophenyl)buta-2,3-dien-1-yl)cyclopent-3-ene-1-carboxamide (232): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)cyclopent-3-ene-1-carboxamide (29.8 mg, 0.2 mmol) and 3-(hydrazonomethyl)benzonitrile, purified by silica gel column chromatography (eluent: 80% Et_2O/hexane) provided the title compound as a yellow amorphous solid (21.2 mg, 0.080 mmol, 40%, 92% *ee*), m.p. 95-96 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (s, 1 H, H7), 7.51 – 7.46 (m, 2 H, H3 and H5), 7.40 (t, *J* = 7.7 Hz, 1 H, H4), 6.26 (dt, *J* = 6.4, 3.2 Hz, 1 H, H8), 5.79 (br s, 1 H, NH), 5.74 (q, *J* = 6.4 Hz, 1 H, H10), 5.64 – 5.58 (m, 2 H, H15 and H16), 4.07 – 4.00 (m, 1 H, H11a), 3.99 – 3.92 (m, 1 H, H11b), 2.92 (qn, *J* = 7.9 Hz, 1 H, H13), 2.59 – 2.52 (m, 4 H, H14 and H17).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.2 (C9), 176.1 (C12), 135.6 (C6), 131.1 (C5), 130.7 (C3), 130.2 (C7), 129.6 (C4), 129.35 (C15/C16), 129.33 (C15/C16), 118.8 (C1), 112.9 (C2), 96.2 (C8), 94.6 (C10), 43.6 (C13), 37.6 (C11), 37.11 (C14/C17), 37.05 (C14/C17).

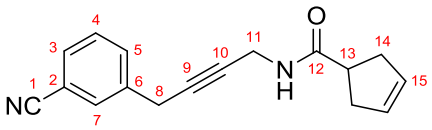
FTIR (ν_{max}, cm^{-1}): 3286 (m, NH), 3058 (w), 2926 (m), 2852 (w), 2231 (m, C≡N), 1956 (w, C=C=C), 1649 (s, C=O), 1536 (s), 1483 (m), 1438 (m), 1340 (w), 1296 (w), 1228 (m), 1181 (w), 899 (w), 871 (w), 842 (w), 801 (m).

HRMS (ESI): calculated for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1335, found 265.1340.

$\boldsymbol{R_f}$ = 0.29 (80% Et_2O/hexane).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -213.1 ($CHCl_3$, *c* = 1.0, 92% *ee*).

HPLC: ChiralART SC, 80:20 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 20.4 (minor), 22.4 (major).



***N*-(4-(3-Cyanophenyl)but-2-yn-1-yl)cyclopent-3-ene-1-carboxamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)cyclopent-3-ene-1-carboxamide and 3-(hydrazonomethyl)benzonitrile, which provided the title compound as an off-white amorphous solid (31.7 mg, 0.120 mmol, 60%), m.p. 91-93 °C.

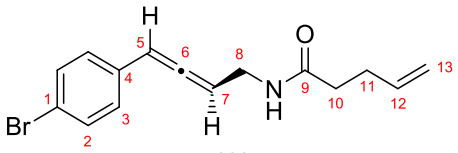
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1 H, H7), 7.56 – 7.51 (m, 2 H, H3 and H5), 7.42 (t, *J* = 7.8 Hz, 1 H, H4), 5.82 (br s, 1 H, NH), 5.67 (s, 2 H, H15), 4.10 (dt, *J* = 5.3, 2.1 Hz, 2 H, H11), 3.62 (t, *J* = 2.1 Hz, 2 H, H8), 2.97 (qn, *J* = 8.1 Hz, 1 H, H13), 2.63 (d, *J* = 8.1 Hz, 4 H, H14).

^{13}C NMR (150 MHz, $CDCl_3$): δ 175.7 (C12), 138.1 (C6), 132.6 (C5), 131.5 (C7), 130.6 (C3), 129.4 (C4), 129.3 (C15), 118.8 (C1), 112.7 (C2), 79.6 (C9), 79.4 (C10), 43.4 (C13), 37.0 (C14), 29.7 (C11), 24.9 (C8).

FTIR (ν_{max}, cm^{-1}): 3287 (m, NH), 3058 (w), 2922 (w), 2851 (w), 2231 (m, C≡N), 1648 (s, C=O), 1584 (w), 1532 (s), 1483 (m), 1435 (m), 1342 (w), 1297 (w), 1228 (m), 1180 (w), 1094 (w), 1038 (w), 946 (w), 900 (w), 844 (m), 788 (m).

HRMS (ESI): calculated for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1335, found 265.1344.

$\boldsymbol{R_f}$ = 0.36 (80% Et_2O/hexane).



233

(*R*)-*N*-(4-(4-Bromophenyl)buta-2,3-dien-1-yl)pent-4-enamide (233): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)pent-4-enamide (27.4 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as an off-white crystalline solid (25.1 mg, 0.082 mmol, 41%, 92% *ee*), m.p. 97-99 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 6.23 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.81 – 5.69 (m, 2 H, H12 and NH), 5.65 (q, *J* = 6.4 Hz, 1 H, H7), 5.01 (dq, *J* = 17.2, 1.2 Hz, 1 H, $H13_{trans}$), 4.94 (dq, *J* = 10.2, 1.2 Hz, 1 H, $H13_{cis}$), 4.04 – 3.89 (m, 2 H, H8), 2.36 – 2.30 (m, 2 H, H11), 2.27 – 2.22 (m, 2 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.6 – 204.5 (br, C6), 172.3 (C9), 137.1 (C12), 132.9 (C4), 131.9 (C2), 128.5 (C3), 121.1 (C1), 115.7 (C13), 96.9 (C5), 93.7 (C7), 37.7 (C8), 35.9 (C10), 29.6 (C11).

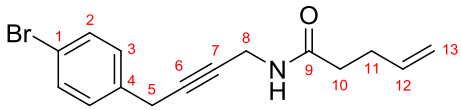
FTIR (ν_{max}, cm^{-1}): 3294 (m, NH), 3079 (w), 2920 (w), 2851 (w), 1952 (w, C=C=C), 1638 (s, C=O), 1538 (s), 1488 (s), 1431 (m), 1381 (w), 1339 (w), 1264 (m), 1230 (m), 1196 (w), 1111 (w), 1070 (m), 1010 (s), 912 (m), 877 (m), 832 (s), 811 (m), 750 (w).

HRMS (ESI): calculated for $C_{15}H_{16}NOBrNa$ $[M+Na]^+$ 328.0307, found 328.0309.

R_f = 0.28 (40% EtOAc/hexane).

$[\alpha]_D^{24.8}$ = -172.5 ($CHCl_3$, *c* = 1.0, 92% *ee*).

HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 32.1 (minor), 33.1 (major).



***N*-(4-(4-Bromophenyl)but-2-yn-1-yl)pent-4-enamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)pent-4-enamide and (4-bromobenzylidene)hydrazine, which provided the title compound as an orange amorphous solid (19.1 mg, 0.062 mmol, 31%), m.p. 68-70 °C.

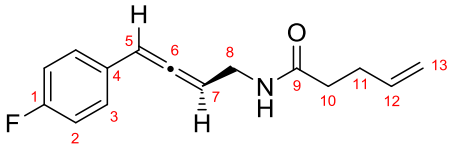
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.19 (d, *J* = 8.4 Hz, 2 H, H3), 5.82 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H, H12), 5.65 (br s, 1 H, NH), 5.07 (dq, *J* = 17.0, 1.4 Hz, 1 H, $H13_{trans}$), 5.01 (dq, *J* = 10.2, 1.4 Hz, 1 H, $H13_{cis}$), 4.08 (dt, *J* = 4.8, 2.2 Hz, 2 H, H8), 3.53 (t, *J* = 2.2 Hz, 2 H, H5), 2.43 – 2.36 (m, 2 H, H11), 2.28 (t, *J* = 7.5 Hz, 2 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9 (C9), 137.0 (C12), 135.6 (C4), 131.7 (C2), 129.8 (C3), 120.7 (C1), 115.9 (C13), 80.9 (C6), 78.3 (C7), 35.7 (C10), 29.8 (C8), 29.6 (C11), 24.7 (C5).

FTIR (ν_{max}, cm^{-1}): 3290 (w, NH), 3078 (w), 2920 (m), 2851 (w), 1641 (s, C=O), 1539 (s), 1487 (s), 1419 (m), 1345 (w), 1266 (m), 1184 (w), 1139 (w), 1110 (w), 1071 (m), 1030 (w), 1012 (s), 914 (m), 840 (m), 801 (m).

HRMS (ESI): calculated for $C_{15}H_{17}NOBr$ $[M+H]^+$ 306.0488, found 306.0485.

***R*$_f$** = 0.36 (40% EtOAc/hexane).



234

(*R*)-*N*-(4-(4-Fluorophenyl)buta-2,3-dien-1-yl)pent-4-enamide (234): Following the general procedure for asymmetric allenylation using *N*-(prop-2-yn-1-yl)pent-4-enamide (27.4 mg, 0.2 mmol) and (4-fluorobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 60% Et_2O/hexane) provided the title compound as a yellow amorphous solid (21.8 mg, 0.089 mmol, 44%, 95% *ee*), m.p. 66-68 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.7, 5.4 Hz, 2 H, H3), 7.00 (t, *J* = 8.7 Hz, 2 H, H2), 6.27 (dt, *J* = 6.5, 3.3 Hz, 1 H, H5), 5.77 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1 H, H12), 5.69 (br s, 1 H, NH), 5.66 (q, *J* = 6.5 Hz, 1 H, H7), 5.01 (dd, *J* = 17.1, 1.4 Hz, 1 H, $H13_{trans}$), 4.94 (dd, *J* = 10.2, 1.4 Hz, 1 H, $H13_{cis}$), 4.05 – 3.89 (m, 2 H, H8), 2.36 – 2.30 (m, 2 H, H11), 2.29 – 2.18 (m, 2 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.3 – 204.2 (br, C6), 172.3 (C9), 162.3 (d, *J* = 246.7 Hz, C1), 137.1 (C12), 129.8 (d, *J* = 3.3 Hz, C4), 128.5 (d, *J* = 8.1 Hz, C3), 115.8 (d, *J* = 22.0 Hz, C2), 115.7 (C13), 96.8 (C5), 93.4 (C7), 37.8 (C8), 35.9 (C10), 29.6 (C11).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.7 (s, 1 F, F1).

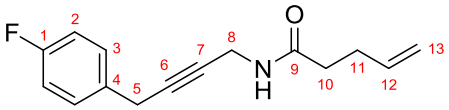
FTIR (ν_{max}, cm^{-1}): 3284 (w, NH), 3072 (w), 2921 (w), 1951 (w, C=C=C), 1643 (m, C=O), 1604 (w), 1543 (m), 1508 (s), 1436 (w), 1394 (w), 1341 (w), 1263 (w), 1225 (m), 1156 (w), 1094 (w), 1014 (w), 996 (w), 916 (w), 876 (w), 838 (m), 765 (w).

HRMS (ESI): calculated for $C_{15}H_{16}FNONa$ $[M+Na]^+$ 268.1108, found 268.1115.

$\boldsymbol{R_f}$ = 0.21 (60% Et_2O/hexane).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25.0}}$ = -212.4 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SA, 97:3 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 35.4 (major), 38.0 (minor).



***N*-(4-(4-Fluorophenyl)but-2-yn-1-yl)pent-4-enamide:** Isolated as the alkyne cross-product from asymmetric allenylation of *N*-(prop-2-yn-1-yl)pent-4-enamide and (4-fluorobenzylidene)hydrazine, which provided the title compound as a yellow amorphous solid (21.3 mg, 0.087 mmol, 43%), m.p. 49-50 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 8.7, 5.4 Hz, 2 H, H3), 7.00 (t, *J* = 8.7 Hz, 2 H, H2), 5.82 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H, H12), 5.67 (br s, 1 H, NH), 5.07 (dd, *J* = 17.0, 1.4 Hz, 1 H, $H13_{trans}$), 5.00 (dd, *J* = 10.2, 1.4 Hz, 1 H, $H13_{cis}$), 4.08 (dt, *J* = 4.8, 2.2 Hz, 2 H, H8), 3.55 (t, *J* = 2.2 Hz, 2 H, H5), 2.43 – 2.36 (m, 2 H, H11), 2.28 (t, *J* = 7.5 Hz, 2 H, H10).

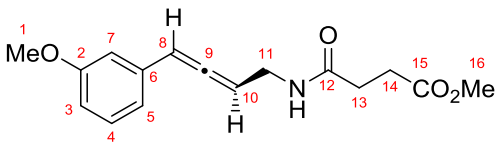
^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9 (C9), 161.9 (d, *J* = 244.8 Hz, C1), 137.0 (C12), 132.2 (d, *J* = 3.2 Hz, C4), 129.5 (d, *J* = 8.0 Hz, C3), 115.8 (C13), 115.5 (d, *J* = 21.5 Hz, C2), 81.4 (C6), 78.1 (C7), 35.7 (C10), 29.8 (C8), 29.6 (C11), 24.5 (C5).

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.4 (s, 1 F, F1).

FTIR (ν_{max}, cm^{-1}): 3281 (w, NH), 3069 (w), 2918 (w), 1642 (m, C=O), 1604 (w), 1539 (m), 1508 (s), 1423 (w), 1345 (w), 1268 (w), 1222 (m), 1158 (w), 1094 (w), 1016 (w), 996 (w), 914 (w), 838 (w), 756 (w).

HRMS (ESI): calculated for $C_{15}H_{16}FNONa$ $[M+Na]^+$ 268.1108, found 268.1114.

$\boldsymbol{R_f}$ = 0.29 (60% Et_2O/hexane).

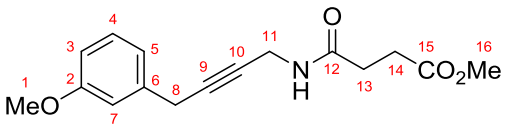


235

Methyl (*R*)-4-((4-(3-methoxyphenyl)buta-2,3-dien-1-yl)amino)-4-oxobutanoate (235): Following the general procedure for asymmetric allenylation using methyl 4-oxo-4-(prop-2-

yn-1-ylamino)butanoate (33.8 mg, 0.2 mmol) and (3-methoxybenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 15% Et_2O/CH_2Cl_2) provided the title compound as a colourless gum (26.2 mg, 0.091 mmol, 45%, 95% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.9 Hz, 1 H, H4), 6.87 (d, *J* = 7.9 Hz, 1 H, H5), 6.84 – 6.82 (m, 1 H, H7), 6.77 (dd, *J* = 7.9, 2.4 Hz, 1 H, H3), 6.26 (dt, *J* = 6.5, 3.3 Hz, 1 H, H8), 5.89 (br s, 1 H, NH), 5.65 (q, *J* = 6.5 Hz, 1 H, H10), 4.03 – 3.90 (m, 2 H, H11), 3.81 (s, 3 H, H1), 3.64 (s, 3 H, H16), 2.66 – 2.58 (m, 2 H, H14), 2.48 – 2.41 (m, 2 H, H13).
^{13}C NMR (150 MHz, $CDCl_3$): δ 204.6 (C9), 173.6 (C15), 171.4 (C12), 160.0 (C2), 135.3 (C6), 129.8 (C4), 119.6 (C5), 113.2 (C3), 112.2 (C7), 97.8 (C8), 93.1 (C10), 55.4 (C1), 51.9 (C16), 38.0 (C11), 31.1 (C13), 29.4 (C14).
FTIR (ν_{max}, cm^{-1}): 3313 (w, NH), 2953 (w), 2838 (w), 1954 (w, C=C=C), 1735 (m, C=O), 1649 (m, C=O), 1597 (m), 1581 (m), 1536 (m), 1490 (m), 1454 (m), 1437 (m), 1408 (w), 1363 (w), 1319 (w), 1260 (s), 1154 (s), 1083 (w), 1039 (m), 994 (w), 946 (w), 875 (m), 846 (m), 785 (m), 754 (m).
HRMS (ESI): calculated for $C_{16}H_{19}NO_4Na$ $[M+Na]^+$ 312.1206, found 312.1213.
R_f = 0.30 (15% Et_2O/CH_2Cl_2).
$[\alpha]_D^{25.0}$ = -190.1 ($CHCl_3$, *c* = 1.0, 95% *ee*).
HPLC: ChiralART SC, 80:20 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 36.1 (minor), 40.2 (major).



Methyl 4-((4-(3-methoxyphenyl)but-2-yn-1-yl)amino)-4-oxobutanoate: Isolated as the alkyne cross-product from asymmetric allenylation of methyl 4-oxo-4-(prop-2-yn-1-ylamino)butanoate and (3-methoxybenzylidene)hydrazine, which provided the title compound as a colourless gum (22.4 mg, 0.077 mmol, 39%).

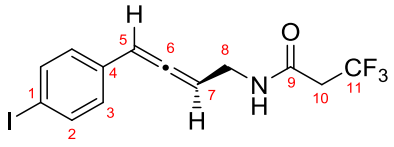
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (t, *J* = 8.0 Hz, 1 H, H4), 6.91 – 6.85 (m, 2 H, H5 and H7), 6.78 (dd, *J* = 8.0, 2.4 Hz, 1 H, H3), 5.88 (br s, 1 H, NH), 4.08 (dt, *J* = 4.8, 2.3 Hz, 2 H, H11), 3.81 (s, 3 H, H1), 3.68 (s, 3 H, H16), 3.56 (t, *J* = 2.3 Hz, 2 H, H8), 2.67 (t, *J* = 6.8 Hz, 2 H, H14), 2.48 (t, *J* = 6.8 Hz, 2 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5 (C15), 171.0 (C12), 159.9 (C2), 138.1 (C6), 129.7 (C4), 120.4 (C5), 113.9 (C3), 112.1 (C7), 81.5 (C9), 77.8 (C10), 55.4 (C1), 52.0 (C16), 30.9 (C13), 30.0 (C11), 29.3 (C14), 25.2 (C8).

FTIR (ν_{max}, cm^{-1}): 3304 (w, NH), 2951 (w), 2837 (w), 1735 (s, C=O), 1649 (s, C=O), 1601 (m), 1586 (m), 1533 (m), 1489 (s), 1453 (m), 1436 (s), 1317 (m), 1257 (s), 1201 (m), 1161 (s), 1080 (w), 1040 (s), 995 (w), 933 (w), 879 (w), 846 (m), 775 (m).

HRMS (ESI): calculated for $C_{16}H_{19}NO_4Na$ $[M+Na]^+$ 312.1206, found 312.1216.

R_f = 0.38 (15% Et_2O/CH_2Cl_2).



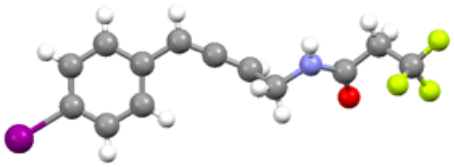
236

(*R*)-3,3,3-Trifluoro-*N*-(4-(4-iodophenyl)buta-2,3-dien-1-yl)propanamide (236): Following the general procedure for asymmetric allenylation using 3,3,3-trifluoro-*N*-(prop-2-yn-1-yl)propanamide (37.1 mg, 0.2 mmol) and (4-iodobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 70% Et_2O/hexane) provided the title compound as an off-white amorphous solid (37.1 mg, 0.097 mmol, 49%, 95% *ee*), m.p. 131-132 °C.

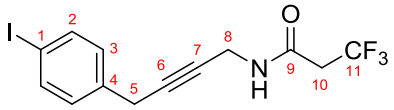
Scale up to 5 mmol was possible using a slightly modified procedure as follows: To a stirred **188**-CuI solution in a 250 mL round-bottomed flask (prepared on the same scale as stated for the stock solution – 51.4 mL, containing 0.15 equiv. ligand, 0.1 equiv. CuI and 2 equiv. Et_3N) was added was added 3,3,3-trifluoro-*N*-(prop-2-yn-1-yl)propanamide (0.825 g, 5.0 mmol, 1.0 equiv.). The mixture was pre-mixed at r.t. for 10 min, forming a clear red-orange homogeneous solution of the copper acetylide-ligand complex. Solutions of hydrazone (0.1 M) and DIPEA (0.2 M) in CH_2Cl_2 were passed through eight pre-conditioned column reactors concurrently (Omnifit® column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g), at a flow rate of 0.5 mL min^{-1} each. When the FlowIR® showed that the intensity of the diazo peak was stable, 12.5 mL of each output stream from the eight columns (2.0 equiv. total with respect to the hydrazone) was directly added into the reaction vial (over 25 min) containing the copper acetylide-ligand complex and the reaction mixture further stirred at r.t. for 10 min. The solution was evaporated under reduced pressure and the residue taken up in CH_2Cl_2 (50 mL). The mixture was washed with concentrated ammonium hydroxide/saturated aqueous NH_4Cl solution (1:9, 50 mL), then the organic layer dried ($MgSO_4$) and evaporated

under reduced pressure. The residue was immediately purified by silica gel column chromatography (eluent: 70% Et_2O/hexane) to provide the title compound as an off-white amorphous solid (0.889 g, 2.33 mmol, 47%, 95% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2 H, H2), 7.00 (d, *J* = 8.3 Hz, 2 H, H3), 6.25 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 6.04 (br s, 1 H, NH), 5.66 (q, *J* = 6.4 Hz, 1 H, H7), 4.07 – 3.92 (m, 2 H, H8), 3.04 (q, *J* = 10.6 Hz, 2 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 162.6 (q, *J* = 3.4 Hz, C9), 137.9 (C2), 133.2 (C4), 128.8 (C3), 124.0 (d, *J* = 276.8 Hz, C11), 97.5 (C5), 92.9 (C7), 92.7 (C1), 41.7 (q, *J* = 29.6 Hz, C10), 38.1 (C8).
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0 (s, 3 F, F11).
FTIR (ν_{max}, cm^{-1}): 3308 (m, NH), 1958 (m, C=C=C), 1652 (s, C=O), 1556 (m), 1486 (w), 1385 (w), 1337 (w), 1268 (w), 1238 (m), 1140 (m), 1107 (m), 1061 (w), 1006 (w), 923 (w), 879 (w), 851 (w), 833 (w).
HRMS (ESI): calculated for $C_{13}H_{12}F_3NOI$ $[M+H]^+$ 381.9910, found 381.9927.
R_f = 0.30 (70% Et_2O/hexane).
$[\alpha]_D^{25.0}$ = -176.5 ($CHCl_3$, *c* = 1.0, 95% *ee*).
HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 16.9 (minor), 18.3 (major).



Slow diffusion of hexane into a saturated solution of **236** in CH_2Cl_2 provided white needle-like crystals suitable for X-ray diffraction analysis. The absolute stereochemistry of the structure was unambiguously confirmed by X-ray crystallography and deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 1514945; space group: $P2_1$; unit cell data: a = 4.8751(2) Å, b = 8.3827(4) Å, c = 34.4135(12) Å, α = 90°, β = 90.295(2)°, γ = 90°; Flack parameter = 0.047(9).



3,3,3-Trifluoro-*N*-(4-(4-iodophenyl)but-2-yn-1-yl)propanamide: Isolated as the alkyne cross-product from asymmetric allenylation of 3,3,3-trifluoro-*N*-(prop-2-yn-1-yl)propanamide and (4-iodobenzylidene)hydrazine, which provided the title compound as an orange amorphous solid (34.4 mg, 0.090 mmol, 45%), m.p. 136-137 °C. During the scale up of **236**, the title compound was also isolated as an off-white amorphous solid (0.821 g, 2.15 mmol, 43%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2 H, H2), 7.05 (d, *J* = 8.3 Hz, 2 H, H3), 6.02 (br s, 1 H, NH), 4.12 (dt, *J* = 4.8, 2.2 Hz, 2 H, H8), 3.53 (t, *J* = 2.2 Hz, 2 H, H5), 3.08 (q, *J* = 10.5 Hz, 2 H, H10).

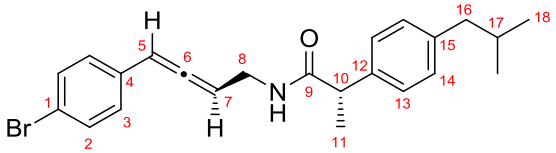
^{13}C NMR (150 MHz, $CDCl_3$): δ 162.3 (q, *J* = 3.4 Hz, C9), 137.8 (C2), 136.1 (C4), 130.0 (C3), 124.0 (q, *J* = 276.8 Hz, C11), 92.1 (C1), 81.6 (C6), 77.3 (C7), 41.6 (q, *J* = 29.7 Hz, C10), 30.3 (C8), 24.8 (C5).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9 (s, 3 F, F11).

FTIR (ν_{max}, cm^{-1}): 3305 (m, NH), 1654 (s, C=O), 1555 (m), 1483 (w), 1451 (w), 1399 (w), 1352 (w), 1278 (w), 1234 (m), 1128 (m), 1111 (m), 1060 (w), 1007 (w), 920 (w), 851 (w), 785 (w).

HRMS (ESI): calculated for $C_{13}H_{12}F_3NOI$ $[M+H]^+$ 381.9910, found 381.9904.

***R*$_f$** = 0.38 (70% Et_2O/hexane).



240

(*S*)-*N*-((*R*)-4-(4-Bromophenyl)buta-2,3-dien-1-yl)-2-(4-isobutylphenyl)propanamide (240): Following the general procedure for asymmetric allenylation using (*S*)-2-(4-isobutylphenyl)-*N*-(prop-2-yn-1-yl)propanamide (48.7 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 50% Et_2O/hexane) provided the title compound as a pale yellow gum (42.2 mg, 0.102 mmol, 51%, 96% *de*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.09 – 7.05 (m, 4 H, H3 and H13), 6.96 (d, *J* = 8.0 Hz, 2 H, H14), 6.11 (dt, *J* = 6.5, 3.7 Hz, 1 H, H5), 5.59 (dt, *J* = 6.5, 5.2 Hz, 1 H, H7), 5.50 (br s, 1 H, NH), 3.90 (td, *J* = 5.2, 3.7 Hz, 2 H, H8), 3.48 (q, *J* = 7.3 Hz, 1 H, H10), 2.39 (d, *J* = 7.2 Hz, 2 H, H16), 1.85 – 1.76 (m, 1 H, H17), 1.48 (d, *J* = 7.3 Hz, 3 H, H11), 0.89 (d, *J* = 6.6 Hz, 6 H, H18).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.2 (C6), 174.5 (C9), 140.9 (C15), 138.1 (C12), 133.0 (C4), 131.9 (C2), 129.7 (C14), 128.4 (C3), 127.6 (C13), 121.1 (C1), 97.3 (C5), 93.9 (C7), 46.9 (C10), 45.1 (C16), 37.4 (C8), 30.3 (C17), 22.5 (C18), 18.5 (C11).

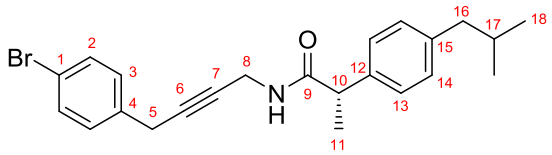
FTIR (ν_{max}, cm^{-1}): 3290 (w, NH), 2954 (m), 2926 (w), 2868 (w), 1953 (w, C=C=C), 1647 (s, C=O), 1541 (m), 1512 (m), 1488 (m), 1464 (w), 1422 (w), 1384 (w), 1366 (w), 1339 (w), 1231 (w), 1192 (w), 1070 (m), 1010 (m), 876 (w), 830 (m).

HRMS (ESI): calculated for $C_{23}H_{26}NOBrNa$ $[M+Na]^+$ 434.1090, found 434.1099.

R_f = 0.23 (50% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = -229.6 ($CHCl_3$, *c* = 0.5, 96% *de*).

HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 26.8 (minor), 28.6 (major).



(*S*)-*N*-(4-(4-Bromophenyl)but-2-yn-1-yl)-2-(4-isobutylphenyl)propanamide: Isolated as the alkyne cross-product from asymmetric allenylation of (*S*)-2-(4-isobutylphenyl)-*N*-(prop-2-yn-1-yl) and (4-bromobenzylidene)hydrazine, after repurification by silica gel column chromatography (eluent: 10% Et_2O/CH_2Cl_2) of the alkyne-containing fractions, which provided the title compound as a pale yellow gum (23.7 mg, 0.057 mmol, 29%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2 H, H2), 7.18 (d, *J* = 8.0 Hz, 2 H, H13), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 7.11 (d, *J* = 8.0 Hz, 2 H, H14), 5.51 (br s, 1 H, NH), 4.09 – 4.02 (m, 1 H, H8a), 4.01 – 3.94 (m, 1 H, H8b), 3.54 (q, *J* = 7.2 Hz, 1 H, H10), 3.48 (t, *J* = 2.2 Hz, 2 H, H5), 2.46 (d, *J* = 7.2 Hz, 2 H, H16), 1.90 – 1.80 (m, 1 H, H17), 1.51 (d, *J* = 7.2 Hz, 3 H, H11), 0.90 (d, *J* = 6.6 Hz, 6 H, H18).

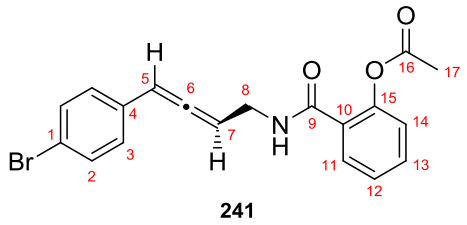
^{13}C NMR (150 MHz, $CDCl_3$): δ 174.2 (C9), 141.0 (C15), 138.3 (C12), 135.6 (C4), 131.7 (C2), 129.8 (C3/C14), 129.7 (C3/C14), 127.5 (C13), 120.6 (C1), 80.7 (C6), 78.4 (C7), 46.7 (C10), 45.1 (C16), 30.3 (C17), 29.9 (C8), 24.7 (C5), 22.5 (C18), 18.6 (C11).

FTIR (ν_{max}, cm^{-1}): 3279 (w, NH), 2955 (m), 2926 (w), 2868 (w), 1647 (s, C=O), 1534 (m), 1511 (m), 1487 (s), 1465 (m), 1420 (m), 1383 (w), 1366 (m), 1263 (w), 1230 (m), 1189 (w), 1071 (m), 1012 (s), 911 (w), 848 (w), 800 (m).

HRMS (ESI): calculated for $C_{23}H_{26}NOBrNa$ $[M+Na]^+$ 434.1090, found 434.1096.

R_f = 0.34 (50% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = -5.5 ($CHCl_3$, *c* = 1.0).



241

(*R*)-2-((4-(4-Bromophenyl)buta-2,3-dien-1-yl)carbamoyl)phenyl acetate (241): Following the general procedure for asymmetric allenylation using 2-(prop-2-yn-1-ylcarbamoyl)phenyl acetate (43.4 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 65% Et_2O/hexane) provided the title compound as an off-white amorphous solid (39.6 mg, 0.103 mmol, 51%, 96% *ee*), m.p. 111-113 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.7, 1.6 Hz, 1 H, H11), 7.47 – 7.43 (m, 1 H, H13), 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.27 – 7.23 (m, 1 H, H12), 7.16 (d, *J* = 8.4 Hz, 2 H, H3), 7.08 (dd, *J* = 8.2, 0.8 Hz, 1 H, H14), 6.44 (br s, 1 H, NH), 6.26 (dt, *J* = 6.2, 3.1 Hz, 1 H, H5), 5.73 (q, *J* = 6.2 Hz, 1 H, H7), 4.18 – 4.07 (m, 2 H, H8), 2.26 (s, 3 H, H17).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.0 – 204.9 (br, C6), 169.3 (C16), 165.8 (C9), 148.1 (C15), 132.8 (C4), 132.0 (C13), 131.9 (C2), 129.7 (C11), 128.6 (C3), 128.3 (C10), 126.4 (C12), 123.3 (C14), 121.2 (C1), 96.9 (C5), 93.2 (C7), 38.3 (C8), 21.2 (C17).

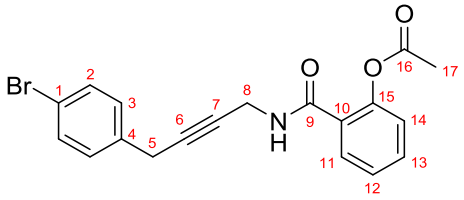
FTIR (ν_{max}, cm^{-1}): 3309 (w, NH), 3073 (w), 2929 (w), 1953 (w, C=C=C), 1767 (m, C=O), 1649 (m, C=O), 1608 (m), 1522 (m), 1487 (m), 1448 (w), 1430 (w), 1368 (m), 1295 (m), 1194 (s), 1099 (w), 1070 (w), 1010 (m), 951 (w), 913 (w), 875 (w), 833 (m), 787 (w), 752 (w).

HRMS (ESI): calculated for $C_{19}H_{16}NO_3BrNa$ $[M+Na]^+$ 408.0206, found 408.0213.

R_f = 0.22 (65% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = -194.2 ($CHCl_3$, *c* = 0.5, 96% *ee*).

HPLC: ChiralART SA, 93:7 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 26.2 (minor), 28.6 (major).



2-((4-(4-Bromophenyl)but-2-yn-1-yl)carbamoyl)phenyl acetate: Isolated as the alkyne cross-product from asymmetric allenylation of 2-(prop-2-yn-1-ylcarbamoyl)phenyl acetate and (4-bromobenzylidene)hydrazine, which provided the title compound as an orange amorphous solid (29.4 mg, 0.076 mmol, 38%), m.p. 105-107 °C.

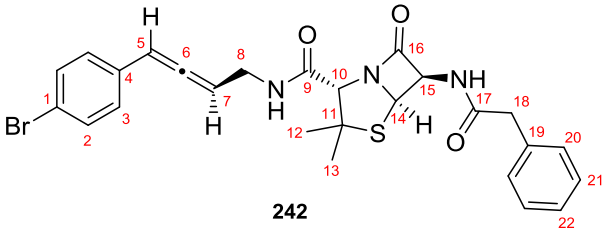
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 7.9, 1.6 Hz, 1 H, H11), 7.48 (td, *J* = 7.9, 1.6 Hz, 1 H, H13), 7.44 (d, *J* = 8.4 Hz, 2 H, H2), 7.31 (td, *J* = 7.9, 1.0 Hz, 1 H, H12), 7.20 (d, *J* = 8.4 Hz, 2 H, H3), 7.11 (dd, *J* = 7.9, 1.0 Hz, 1 H, H14), 6.49 (br s, 1 H, NH), 4.25 (dt, *J* = 4.8, 2.3 Hz, 2 H, H8), 3.56 (t, *J* = 2.3 Hz, 2 H, H5), 2.25 (s, 3 H, H17).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.1 (C16), 165.1 (C9), 148.1 (C15), 135.5 (C4), 132.2 (C13), 131.8 (C2), 130.2 (C11), 129.8 (C3), 127.7 (C10), 126.5 (C12), 123.4 (C14), 120.7 (C1), 81.3 (C6), 78.1 (C7), 30.3 (C8), 24.7 (C5), 21.0 (C17).

FTIR (ν_{max}, cm^{-1}): 3303 (w, NH), 3064 (w), 2929 (w), 1768 (m, C=O), 1650 (m, C=O), 1608 (m), 1520 (m), 1486 (m), 1448 (w), 1421 (w), 1368 (m), 1292 (m), 1194 (s), 1099 (m), 1071 (w), 1045 (w), 1012 (m), 978 (w), 954 (w), 913 (w), 836 (m), 799 (m), 751 (m).

HRMS (ESI): calculated for $C_{19}H_{16}NO_3BrNa$ $[M+Na]^+$ 408.0206, found 408.0210.

***R*$_f$** = 0.27 (65% Et_2O/hexane).



242

(2*S*,5*R*,6*R*)-*N*-((*R*)-4-(4-Bromophenyl)buta-2,3-dien-1-yl)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide (242): Following the general procedure for asymmetric allenylation using (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-

phenylacetamido)-*N*-(prop-2-yn-1-yl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide (74.3 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, stirred for 20 min after addition of diazo compound, purified by silica gel column chromatography (eluent: 90% Et_2O/hexane) provided the title compound as an off-white foam (32.0 mg, 0.059 mmol, 30%, 98% *de*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.36 (t, *J* = 7.3 Hz, 2 H, H21), 7.31 (t, *J* = 7.3 Hz, 1 H, H22), 7.23 (d, *J* = 7.3 Hz, 2 H, H20), 7.13 (d, *J* = 8.4 Hz, 2 H, H3), 6.59 (br t, *J* = 5.7 Hz, 1 H, C8-NH), 6.23 (dt, *J* = 6.3, 3.2 Hz, 1 H, H5), 6.03 (br d, *J* = 9.2 Hz, 1 H, C15-NH), 5.66 – 5.59 (m, 2 H, H7 and H15), 5.19 (d, *J* = 4.5 Hz, 1 H, H14), 4.02 (s, 1 H, H10), 4.02 – 3.97 (m, 1 H, H8a), 3.94 – 3.87 (m, 1 H, H8b), 3.63 – 3.56 (m, 2 H, H18), 1.66 (s, 3 H, H12/H13), 1.46 (s, 3 H, H12/H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.9 (C6), 176.4 (C16), 170.5 (C17), 167.2 (C9), 133.7 (C19), 132.6 (C4), 132.0 (C2), 129.5 (C20), 129.3 (C21), 128.5 (C3), 127.9 (C22), 121.4 (C1), 97.3 (C5), 93.1 (C7), 72.8 (C10), 66.2 (C14), 64.7 (C11), 57.2 (C15), 43.4 (C18), 37.6 (C8), 28.4 (C12/C13), 26.7 (C12/C13).

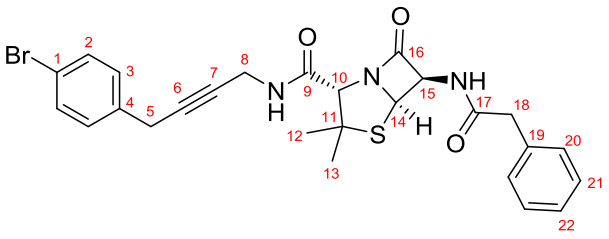
FTIR (ν_{max}, cm^{-1}): 3294 (w, NH), 3031 (w), 2964 (w), 1956 (w, C=C=C), 1782 (m, C=O), 1655 (s, C=O), 1598 (w), 1508 (m), 1489 (m), 1455 (w), 1431 (w), 1390 (w), 1368 (w), 1288 (m), 1234 (w), 1159 (w), 1129 (w), 1102 (w), 1070 (m), 1031 (w), 1010 (m), 909 (m), 833 (s).

HRMS (ESI): calculated for $C_{26}H_{26}N_3O_3SBrNa$ $[M+Na]^+$ 562.0770, found 562.0782.

R_f = 0.24 (90% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = +2.2 ($CHCl_3$, *c* = 0.2, 98% *de*).

HPLC: ChiralART SC, 85:15 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 30.3 (major), 33.3 (minor).



(2*S*,5*R*,6*R*)-*N*-(4-(4-Bromophenyl)but-2-yn-1-yl)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide: Isolated as the alkyne cross-product from asymmetric allenylation of (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-*N*-(prop-2-yn-1-yl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide and

(4-bromobenzylidene)hydrazine, which provided the title compound as an orange foam (30.3 mg, 0.056 mmol, 28%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.38 (t, *J* = 7.4 Hz, 2 H, H21), 7.32 (t, *J* = 7.4 Hz, 1 H, H22), 7.25 (d, *J* = 7.4 Hz, 2 H, H20), 7.18 (d, *J* = 8.4 Hz, 2 H, H3), 6.59 (br t, *J* = 5.2 Hz, 1 H, C8-NH), 6.11 (br d, *J* = 9.3 Hz, 1 H, C15-NH), 5.77 (dd, *J* = 9.3, 4.5 Hz, 1 H, H15), 5.35 (d, *J* = 4.5 Hz, 1 H, H14), 4.14 – 4.08 (m, 2 H, H8a and H10), 4.00 (ddt, *J* = 17.5, 4.8, 2.2 Hz, 1 H, H8b), 3.66 – 3.58 (m, 2 H, H18), 3.53 (t, *J* = 2.2 Hz, 2 H, H5), 1.69 (s, 3 H, H12/H13), 1.47 (s, 3 H, H12/H13).

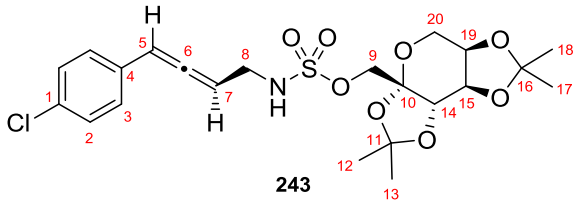
^{13}C NMR (150 MHz, $CDCl_3$): δ 176.6 (C16), 170.6 (C17), 167.1 (C9), 135.4 (C4), 133.7 (C19), 131.8 (C2), 129.7 (C3), 129.5 (C20), 129.3 (C21), 127.9 (C22), 120.7 (C1), 81.3 (C6), 77.6 (C7), 72.6 (C10), 66.3 (C14), 64.9 (C11), 57.3 (C15), 43.4 (C18), 29.6 (C8), 28.3 (C12/C13), 26.6 (C12/C13), 24.7 (C5).

FTIR (ν_{max}, cm^{-1}): 3295 (w, NH), 3061 (w), 2967 (w), 1785 (m, C=O), 1657 (s, C=O), 1520 (m), 1488 (m), 1455 (w), 1420 (w), 1293 (w), 1238 (w), 1129 (w), 1071 (w), 1030 (w), 1012 (w), 910 (w), 841 (w).

HRMS (ESI): calculated for $C_{26}H_{26}N_3O_3SBrNa$ $[M+Na]^+$ 562.0770, found 562.0774.

R_f = 0.30 (90% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = +145.0 ($CHCl_3$, *c* = 0.2).



243

((3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3a-yl)methyl ((*R*)-4-(4-chlorophenyl)buta-2,3-dien-1-yl)sulfamate (243): Following the general procedure for asymmetric allenylation using ((3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3a-yl)methyl prop-2-yn-1-ylsulfamate (75.5 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 60% Et_2O/hexane) provided a nearly inseparable mixture of the title compound and the alkyne cross-product as a colourless gum (96.5 mg containing 56.8 mg of the allene, 0.113 mmol, 57%, 96% *de*). An analytical sample of the

allene could be obtained by repeated purification by silica gel column chromatography (eluent: 50% Et_2O/hexane).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.21 (d, *J* = 8.5 Hz, 2 H, H3), 6.31 (dt, *J* = 6.1, 3.0 Hz, 1 H, H5), 5.74 (q, *J* = 6.1 Hz, 1 H, H7), 4.70 (br t, *J* = 5.9 Hz, 1 H, NH), 4.61 (dd, *J* = 7.9, 2.6 Hz, 1 H, H15), 4.32 (d, *J* = 2.6 Hz, 1 H, H14), 4.25 – 4.23 (m, 1 H, H19), 4.22 (d, *J* = 10.5 Hz, 1 H, H9a), 4.15 (d, *J* = 10.5 Hz, 1 H, H9b), 3.91 – 3.86 (m, 3 H, H8 and H20a), 3.76 (d, *J* = 13.0 Hz, 1 H, H20b), 1.53 (s, 3 H, H12/H13), 1.47 (s, 3 H, H17/H18), 1.41 (s, 3 H, H12/H13), 1.34 (s, 3 H, H17/H18).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.1 (C6), 133.4 (C1), 131.8 (C4), 129.1 (C2), 128.3 (C3), 109.40 (C11), 109.36 (C16), 101.0 (C10), 97.3 (C5), 92.3 (C7), 70.7 (C14), 70.6 (C9), 70.5 (C19), 70.0 (C15), 61.5 (C20), 42.3 (C8), 26.6 (C12/C13), 26.0 (C17/C18), 25.3 (C12/C13), 24.1 (C17/C18).

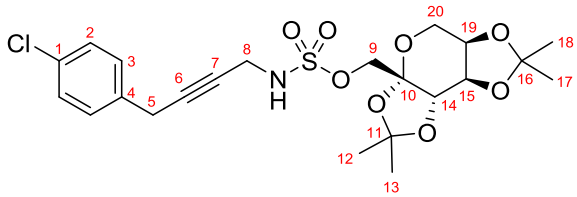
FTIR (ν_{max}, cm^{-1}): 3286 (br w, NH), 2991 (w), 2937 (w), 1954 (w, C=C=C), 1492 (w), 1455 (w), 1371 (m), 1319 (w), 1252 (m), 1205 (m), 1172 (s), 1070 (s), 1012 (s), 980 (m), 912 (m), 885 (s), 865 (s), 833 (s), 803 (s), 755 (s).

HRMS (ESI): calculated for $C_{22}H_{28}NO_8SClNa$ $[M+Na]^+$ 524.1116, found 524.1123.

R_f = 0.38 (60% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = -124.6 ($CHCl_3$, *c* = 1.0, 96% *de*).

HPLC: ChiralART SC, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 32.5 (minor), 34.4 (major).



((3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3a-yl)methyl (4-(4-chlorophenyl)but-2-yn-1-yl)sulfamate: Isolated as the alkyne cross-product from asymmetric allenylation of ((3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3a-yl)methyl prop-2-yn-1-ylsulfamate and (4-chlorobenzylidene)hydrazine (**62**) as part of the colourless gum (96.5 mg containing 39.7 mg of the alkyne, 0.079 mmol, 40%). An analytical sample of the alkyne could be obtained by purification by $AgNO_3$-impregnated silica gel (10% w/w $AgNO_3/SiO_2$,

eluent: 50% Et_2O/hexane). (N.B. The allene decomposes during purification with $AgNO_3$-impregnated silica gel).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2 H, H2), 7.24 (d, *J* = 8.4 Hz, 2 H, H3), 4.72 (br t, *J* = 5.7 Hz, 1 H, NH), 4.59 (dd, *J* = 7.9, 2.6 Hz, 1 H, H15), 4.32 (d, *J* = 2.6 Hz, 1 H, H14), 4.25 (d, *J* = 10.5 Hz, 1 H, H9a), 4.24 – 4.22 (m, 1 H, H19), 4.17 (d, *J* = 10.5 Hz, 1 H, H9b), 4.01 – 3.98 (m, 2 H, H8), 3.89 (dd, *J* = 13.0, 1.8 Hz, 1 H, H20a), 3.76 (d, *J* = 13.0 Hz, 1 H, H20b), 3.58 (t, *J* = 2.0 Hz, 2 H, H5), 1.53 (s, 3 H, H12/H13), 1.47 (s, 3 H, H17/H18), 1.41 (s, 3 H, H12/H13), 1.34 (s, 3 H, H17/H18).

^{13}C NMR (150 MHz, $CDCl_3$): δ 134.6 (C4), 132.8 (C1), 129.4 (C3), 128.9 (C2), 109.40 (C11), 109.36 (C16), 101.0 (C10), 83.1 (C6), 76.7 (C7), 70.8 (C9), 70.7 (C19), 70.5 (C14), 70.0 (C15), 61.5 (C20), 34.2 (C8), 26.6 (C12/C13), 26.0 (C17/C18), 25.3 (C12/C13), 24.6 (C5), 24.2 (C17/C18).

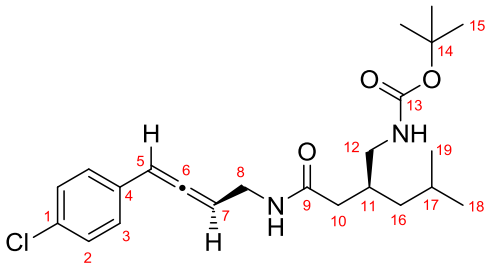
FTIR (ν_{max}, cm^{-1}): 3288 (w, NH), 2989 (w), 2937 (w), 1492 (w), 1456 (w), 1372 (m), 1319 (w), 1252 (m), 1206 (m), 1176 (s), 1101 (m), 1070 (s), 1014 (s), 948 (w), 913 (m), 885 (m), 865 (m), 831 (m), 804 (m), 754 (s).

HRMS (ESI): calculated for $C_{22}H_{28}NO_8SClNa$ $[M+Na]^+$ 524.1116, found 524.1122.

R_f = 0.39 (60% Et_2O/hexane).

$[\alpha]_D^{29.5}$ = -34.8 ($CHCl_3$, *c* = 1.0).

(**Procedure for generation of $AgNO_3$-impregnated silica gel:** To a solution of $AgNO_3$ (2.0 g) in 75% aqueous EtOH (80 mL) in an amber glass 100 mL round-bottomed flask was added silica gel (20 g, 230-400 mesh, pore size 60 Å). The mixture was sonicated for 10 min with manual stirring. The solvent was then removed under reduced pressure on a rotary evaporator (60 °C water bath temperature, 40 mmHg), then dried at 140 °C for 2 h.)



244

***tert*-Butyl ((*S*)-2-(2-(((*R*)-4-(4-chlorophenyl)buta-2,3-dien-1-yl)amino)-2-oxoethyl)-4-methylpentyl)carbamate (244):** Following the general procedure for asymmetric

allenylation using *tert*-butyl (*S*)-(4-methyl-2-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)pentyl)carbamate (59.3 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine (**62**), purified by silica gel column chromatography (eluent: 10% Et_2O/CH_2Cl_2) provided the title compound as a colourless gum (38.7 mg, 0.092 mmol, 46%, 96% *de*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2 H, H2), 7.20 (d, *J* = 8.6 Hz, 2 H, H3), 6.87 (br s, 1 H, C8-NH), 6.23 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.68 (q, *J* = 6.4 Hz, 1 H, H7), 4.79 (br s, 1 H, C12-NH), 4.07 – 4.00 (m, 1 H, H8a), 3.97 – 3.89 (m, 1 H, H8b), 3.19 (ddd, *J* = 14.2, 6.6, 3.9 Hz, 1 H, H12a), 2.96 (dt, *J* = 14.2, 6.6 Hz, 1 H, H12b), 2.12 – 2.03 (m, 2 H, H10), 2.01 – 1.93 (m, 1 H, H11), 1.62 – 1.55 (m, 1 H, H17), 1.42 (s, 9 H, H15), 1.10 – 1.05 (m, 2 H, H16), 0.87 – 0.81 (m, 6 H, H18 and H19).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.9 (C6), 172.4 (C9), 157.1 (C13), 132.9 (C1), 132.7 (C4), 128.9 (C2), 128.2 (C3), 96.6 (C5), 93.7 (C7), 79.6 (C14), 43.5 (C12), 41.7 (C16), 39.4 (C10), 37.9 (C8), 34.6 (C11), 28.5 (C15), 25.3 (C17), 22.8 (C18/C19), 22.7 (C18/C19).

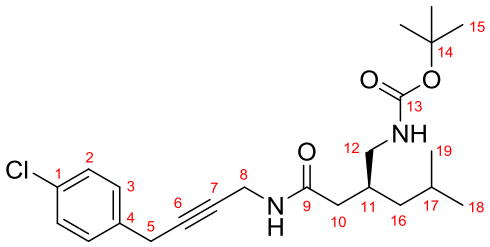
FTIR (ν_{max}, cm^{-1}): 3300 (m, NH), 2957 (m), 2930 (m), 2871 (m), 1953 (w, C=C=C), 1691 (s, C=O), 1648 (s, C=O), 1535 (s), 1492 (s), 1453 (m), 1391 (m), 1366 (m), 1251 (m), 1169 (s), 1091 (m), 1014 (w), 874 (w), 834 (m).

HRMS (ESI): calculated for $C_{23}H_{34}N_2O_3Cl$ $[M+H]^+$ 421.2252, found 421.2255.

R_f = 0.30 (10% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -175.2 ($CHCl_3$, *c* = 1.0, 96% *de*).

HPLC: ChiralART SA, 95:5 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 15.9 (minor), 16.8 (major).



***tert*-Butyl (*S*)-(2-(2-((4-(4-chlorophenyl)but-2-yn-1-yl)amino)-2-oxoethyl)-4-methylpentyl)carbamate:** Isolated as the alkyne cross-product from asymmetric allenylation of *tert*-butyl (*S*)-(4-methyl-2-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)pentyl)carbamate and (4-chlorobenzylidene)hydrazine (**62**), which provided the title compound as a colourless gum (34.6 mg, 0.082 mmol, 41%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 – 7.24 (m, 4 H, H2 and H3), 6.90 (br s, 1 H, C8-NH), 4.84 (br s, 1 H, C12-NH), 4.13 – 4.03 (m, 2 H, H8), 3.55 (t, *J* = 2.0 Hz, 2 H, H5), 3.23 (ddd, *J* = 14.2, 6.5, 3.9 Hz, 1 H, H12a), 3.00 (dt, *J* = 14.2, 6.5 Hz, 1 H, H12b), 2.17 – 2.09 (m, 2 H, H10), 2.07 – 1.99 (m, 1 H, H11), 1.68 – 1.60 (m, 1 H, H17), 1.43 (s, 9 H, H15), 1.13 (t, *J* = 7.1 Hz, 2 H, H16), 0.90 – 0.87 (m, 6 H, H18 and H19).

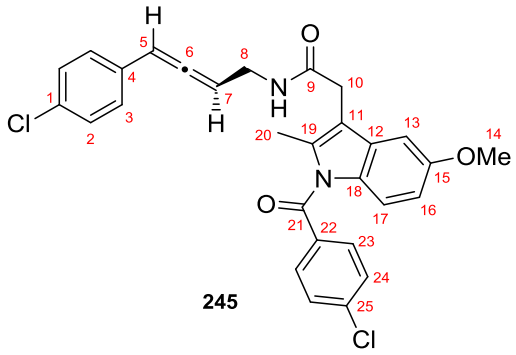
^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3 (C9), 157.1 (C13), 135.2 (C4), 132.5 (C1), 129.4 (C3), 128.7 (C2), 80.5 (C6), 79.7 (C14), 78.6 (C7), 43.5 (C12), 41.7 (C16), 39.2 (C10), 34.6 (C11), 29.7 (C8), 28.5 (C15), 25.3 (C17), 24.6 (C5), 22.9 (C18/C19), 22.8 (C18/C19).

FTIR (ν_{max}, cm^{-1}): 3323 (m, NH), 2958 (m), 2930 (m), 1691 (s, C=O), 1649 (s, C=O), 1531 (s), 1492 (s), 1453 (m), 1391 (m), 1366 (m), 1251 (m), 1169 (s), 1091 (m), 1016 (m), 806 (w).

HRMS (ESI): calculated for $C_{23}H_{33}N_2O_3ClNa$ $[M+Na]^+$ 443.2072, found 443.2069.

R_f = 0.39 (10% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -12.2 ($CHCl_3$, *c* = 1.0).



245

(*R*)-2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(4-(4-chlorophenyl)-buta-2,3-dien-1-yl)acetamide (245): Following the general procedure for asymmetric allenylation using 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(prop-2-yn-1-yl)acetamide (79.0 mg, 0.2 mmol) and (4-chlorobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 5% Et_2O/CH_2Cl_2) provided the title compound as a yellow foam (41.8 mg, 0.080 mmol, 40%, 95% *ee*). (N.B. The starting material is sparingly soluble in reaction mixture at the start and thus the reaction mixture appears as a yellow-orange suspension, but solubilises over time as the diazo compound is added).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.5 Hz, 2 H, H23), 7.46 (d, *J* = 8.5 Hz, 2 H, H24), 7.16 (d, *J* = 8.4 Hz, 2 H, H2), 6.99 (d, *J* = 8.4 Hz, 2 H, H3), 6.82 (d, *J* = 2.4 Hz, 1 H, H13), 6.73 (d, *J* = 9.0 Hz, 1 H, H17), 6.65 (dd, *J* = 9.0, 2.4 Hz, 1 H, H16), 6.02 (dt, *J* = 6.3,

3.6 Hz, 1 H, H5), 5.80 (br t, *J* = 5.1 Hz, 1 H, NH), 5.61 (q, *J* = 6.3 Hz, 1 H, H7), 3.98 – 3.85 (m, 2 H, H8), 3.78 (s, 3 H, H14), 3.60 (AB q, *J* = 17.4 Hz, 2 H, H10), 2.25 (s, 3 H, H20).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.8 (C6), 169.8 (C21), 168.2 (C9), 156.3 (C15), 139.7 (C25), 136.5 (C19), 133.5 (C22), 133.0 (C1), 132.0 (C4), 131.3 (C23), 130.9 (C18), 130.3 (C12), 129.3 (C24), 128.9 (C2), 128.0 (C3), 115.2 (C17), 112.6 (C11), 112.2 (C16), 100.9 (C13), 97.4 (C5), 93.4 (C7), 55.9 (C14), 37.5 (C8), 32.2 (C10), 13.2 (C20).

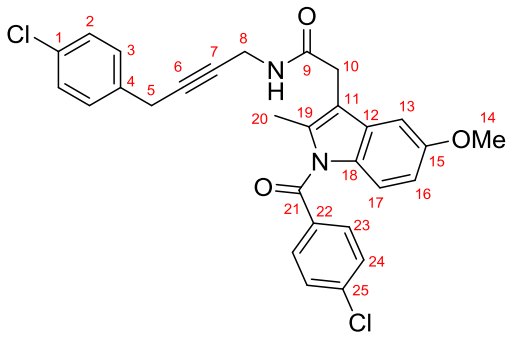
FTIR (ν_{max}, cm^{-1}): 3304 (w, NH), 3062 (w), 2930 (w), 2834 (w), 1953 (w, C=C=C), 1674 (s, C=O), 1651 (s, C=O), 1591 (m), 1521 (m), 1490 (m), 1477 (s), 1456 (m), 1436 (m), 1401 (w), 1357 (s), 1317 (s), 1289 (m), 1260 (m), 1223 (s), 1179 (m), 1149 (m), 1089 (s), 1070 (m), 1037 (m), 1014 (m), 993 (w), 925 (m), 909 (m), 877 (w), 832 (s), 754 (m).

HRMS (ESI): calculated for $C_{29}H_{24}N_2O_3Cl_2Na$ $[M+Na]^+$ 541.1056, found 541.1065.

R_f = 0.27 (5% Et_2O/CH_2Cl_2).

$[\alpha]_D^{25.0}$ = -171.8 ($CHCl_3$, *c* = 1.0, 95% *ee*).

HPLC: ChiralART SA, 85:15 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 21.2 (major), 30.1 (minor).



2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(4-(4-chlorophenyl)but-2-yn-1-yl)acetamide: Isolated as the alkyne cross-product from asymmetric allenylation of 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(prop-2-yn-1-yl)acetamide and (4-chlorobenzylidene)hydrazine, which provided the title compound as a pale yellow amorphous solid (39.6 mg, 0.076 mmol, 38%), m.p. 195-197 °C.

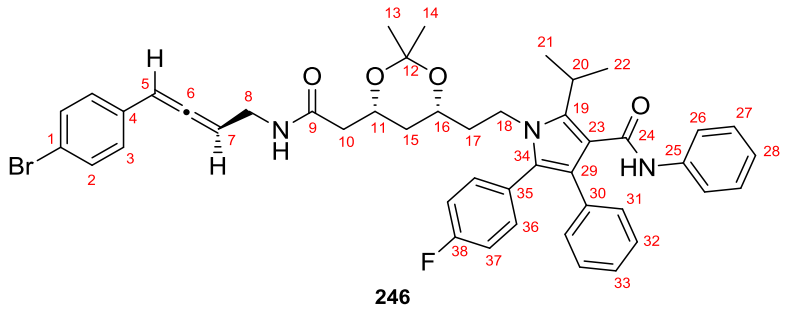
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.6 Hz, 2 H, H23), 7.48 (d, *J* = 8.6 Hz, 2 H, H24), 7.24 (d, *J* = 8.5 Hz, 2 H, H2), 7.16 (d, *J* = 8.5 Hz, 2 H, H3), 6.88 (d, *J* = 2.5 Hz, 1 H, H13), 6.86 (d, *J* = 9.1 Hz, 1 H, H17), 6.71 (dd, *J* = 9.1, 2.5 Hz, 1 H, H16), 5.74 (br t, *J* = 5.3 Hz, 1 H, NH), 4.05 (dt, *J* = 5.3, 2.2 Hz, 2 H, H8), 3.79 (s, 3 H, H14), 3.66 (s, 2 H, H10), 3.49 (t, *J* = 2.2 Hz, 2 H, H5), 2.38 (s, 3 H, H20).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6 (C21), 168.5 (C9), 156.4 (C15), 139.8 (C25), 136.6 (C19), 134.9 (C4), 133.6 (C22), 132.6 (C1), 131.3 (C23), 131.0 (C18), 130.3 (C12), 129.4 (C24), 129.3 (C3), 128.8 (C2), 115.2 (C17), 112.54 (C11), 112.46 (C16), 101.0 (C13), 80.9 (C6), 78.1 (C7), 55.9 (C14), 32.2 (C10), 29.8 (C8), 24.6 (C5), 13.4 (C20).

FTIR (ν_{max}, cm^{-1}): 3296 (m, NH), 2930 (w), 1670 (m), 1628 (s, C=O), 1538 (m), 1490 (m), 1477 (m), 1438 (m), 1400 (m), 1361 (s), 1326 (s), 1288 (m), 1259 (m), 1221 (s), 1177 (w), 1151 (m), 1089 (s), 1073 (m), 1035 (m), 1013 (m), 992 (w), 914 (w), 833 (m), 792 (m), 754 (m).

HRMS (ESI): calculated for $C_{29}H_{24}N_2O_3Cl_2Na$ $[M+Na]^+$ 541.1056, found 541.1067.

***R*$_f$** = 0.41 (5% Et_2O/CH_2Cl_2).



1-(2-((4*R*,6*R*)-6-(2-(((*R*)-4-(4-Bromophenyl)buta-2,3-dien-1-yl)amino)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (246): Following the general procedure for asymmetric allenylation using 1-(2-((4*R*,6*R*)-2,2-dimethyl-6-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (127.2 mg, 0.2 mmol) and (4-bromobenzylidene)hydrazine, purified by silica gel column chromatography (eluent: 85% Et_2O/hexane) provided the title compound as an off-white foam (64.8 mg, 0.081 mmol, 40%, 94% *de*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2 H, H2), 7.22 – 7.14 (m, 9 H, H27, H31, H32, H33 and H36), 7.13 (d, *J* = 8.4 Hz, 2 H, H3), 7.07 (d, *J* = 7.9 Hz, 2 H, H26), 7.01 – 6.96 (m, 3 H, H28 and H37), 6.87 (br s, 1 H, C24-NH), 6.29 (br t, *J* = 5.7 Hz, 1 H, C8-NH), 6.21 (dt, *J* = 6.4, 3.2 Hz, 1 H, H5), 5.65 (q, *J* = 6.4 Hz, 1 H, H7), 4.09 – 3.99 (m, 3 H, H8a, H11 and H18a), 3.92 – 3.86 (m, 1 H, H8b), 3.84 – 3.77 (m, 1 H, H18b), 3.65 – 3.59 (m, 1 H, H16), 3.59 – 3.53 (m, 1 H, H20), 2.32 (dd, *J* = 15.1, 7.6 Hz, 1 H, H10a), 2.23 (dd, *J* = 15.1, 4.1 Hz, 1 H, H10b), 1.69 – 1.59 (m, 2 H, H17), 1.52 (superimposed d, *J* = 7.1 Hz, 6 H, H21 and H22),

1.30 – 1.27 (s superimposed on m, 4 H, H13/H14 and H15a), 1.26 (s, 3 H, H13/H14), 1.04 (dt, *J* = 12.8, 11.7 Hz, 1 H, H15b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 204.7 (C6), 170.4 (C9), 164.9 (C24), 162.4 (d, *J* = 247.9 Hz, C38), 141.6 (C19), 138.5 (C25), 134.7 (C30), 133.3 (d, *J* = 8.1 Hz, C36), 132.9 (C4), 131.9 (C2), 130.6 (C31), 128.9 (C34), 128.8 (C32), 128.49 (C3/C27), 128.48 (C3/C27), 128.4 (d, *J* = 3.2 Hz, C35), 126.7 (C33), 123.6 (C28), 121.9 (C29), 121.1 (C1), 119.7 (C26), 115.50 (d, *J* = 21.4 Hz, C37), 115.49 (C23), 99.0 (C12), 96.8 (C5), 93.6 (C7), 66.4 (C16), 66.2 (C11), 43.3 (C10), 40.9 (C18), 38.1 (C17), 37.7 (C8), 36.0 (C15), 30.0 (C13/C14), 26.2 (C20), 21.9 (C21/C22), 21.7 (C21/C22), 19.8 (C13/C14).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.6 (s, 1 F, F38).

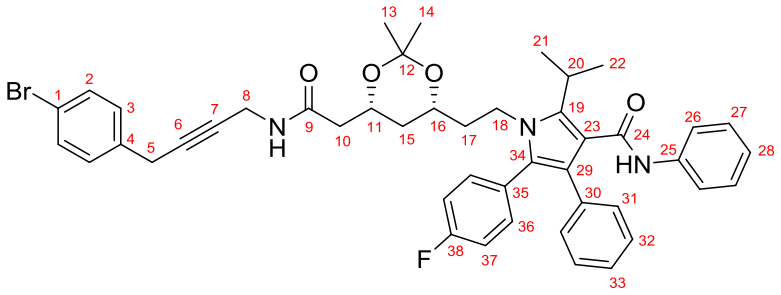
FTIR (ν_{max}, cm^{-1}): 3301 (w, NH), 2961 (w), 1957 (w, C=C=C), 1652 (s, C=O), 1595 (m), 1526 (s), 1509 (s), 1488 (s), 1436 (s), 1381 (m), 1313 (s), 1224 (m), 1201 (m), 1170 (m), 1157 (s), 1115 (w), 1070 (w), 1032 (w), 1010 (w), 942 (w), 909 (m), 838 (m), 753 (m).

HRMS (ESI): calculated for $C_{46}H_{48}FN_3O_4Br$ $[M+H]^+$ 804.2807, found 804.2822.

R_f = 0.31 (85% Et_2O/hexane).

$[\alpha]_D^{25.0}$ = -78.7 ($CHCl_3$, *c* = 1.0, 94% *de*).

HPLC: ChiralART SC, 85:15 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 254 nm; t_R (min) = 32.8 (minor), 38.0 (major).



1-(2-((*4R*,6*R*)-6-(2-((4-(4-Bromophenyl)but-2-yn-1-yl)amino)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide: Isolated as the alkyne cross-product from asymmetric allenylation of 1-(2-((4*R*,6*R*)-2,2-dimethyl-6-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide and (4-bromobenzyl-idene)hydrazine, which provided the title compound as an orange foam (65.1 mg, 0.081 mmol, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2 H, H2), 7.21 – 7.13 (m, 11 H, H3, H27, H31, H32, H33 and H36), 7.07 (d, *J* = 7.8 Hz, 2 H, H26), 7.01 – 6.96 (m, 3 H, H28 and H37), 6.87 (br s, 1 H, C24-NH), 6.37 (br t, *J* = 5.0 Hz, 1 H, C8-NH), 4.16 – 4.10 (m, 1 H, H11), 4.10 – 4.00 (m, 3 H, H8 and H18a), 3.86 – 3.78 (m, 1 H, H18b), 3.70 – 3.64 (m, 1 H, H16), 3.60 – 3.54 (m, 1 H, H20), 3.52 (t, *J* = 2.1 Hz, 2 H, H5), 2.33 (dd, *J* = 15.1, 7.6 Hz, 1 H, H10a), 2.26 (dd, *J* = 15.1, 4.0 Hz, 1 H, H10b), 1.70 – 1.60 (m, 2 H, H17), 1.53 (superimposed d, *J* = 7.1 Hz, 6 H, H21 and H22), 1.33 (s, 3 H, H13/H14), 1.32 – 1.27 (s superimposed on m, 4 H, H13/H14 and H15a), 1.07 (dt, *J* = 12.8, 11.7 Hz, 1 H, H15b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.0 (C9), 164.9 (C24), 162.4 (d, *J* = 247.9 Hz, C38), 141.6 (C19), 138.5 (C25), 135.6 (C4), 134.7 (C30), 133.3 (d, *J* = 8.1 Hz, C36), 131.7 (C2), 130.6 (C31), 129.7 (C3), 128.9 (C34), 128.8 (C32), 128.5 (C27), 128.4 (d, *J* = 3.3 Hz, C35), 126.7 (C33), 123.6 (C28), 121.9 (C29), 120.6 (C1), 119.7 (C26), 115.49 (d, *J* = 21.4 Hz, C37), 115.48 (C23), 99.0 (C12), 80.7 (C6), 78.3 (C7), 66.5 (C16), 66.2 (C11), 42.9 (C10), 40.9 (C18), 38.0 (C17), 35.9 (C15), 30.0 (C13/C14), 29.6 (C8), 26.2 (C20), 24.7 (C5), 21.9 (C21/C22), 21.7 (C21/C22), 19.9 (C13/C14).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.6 (s, 1 F, F38).

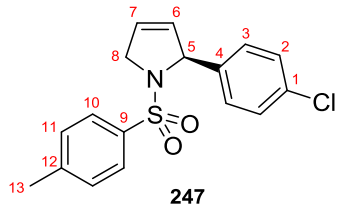
FTIR (ν_{max}, cm^{-1}): 3301 (w, NH), 2960 (w), 1654 (s, C=O), 1596 (m), 1527 (s), 1509 (s), 1488 (s), 1437 (m), 1381 (m), 1314 (m), 1224 (m), 1201 (m), 1157 (m), 1073 (w), 1032 (w), 1013 (m), 942 (w), 910 (m), 886 (w), 841 (m), 805 (w), 754 (m).

HRMS (ESI): calculated for $C_{46}H_{48}FN_3O_4Br$ $[M+H]^+$ 804.2807, found 804.2817.

$\boldsymbol{R_f}$ = 0.40 (85% Et_2O/hexane).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25.0}}$ = -7.8 ($CHCl_3$, *c* = 1.0).

5.3.6. Synthetic procedure and characterisation for silver-mediated cyclisation



247

(*S*)-2-(4-Chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (247): In the dark, to a solution of (*R*)-*N*-(4-(4-chlorophenyl)buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (**(*R*)-65**) (12.3 mg, 0.037 mmol, 1 equiv., 97% *ee*) in CH_2Cl_2 (0.3 mL) was added a solution of $AgPF_6$ (1.0 mg, 0.004 mmol, 0.1 equiv.) in CH_2Cl_2 (0.05 mL). The mixture was stirred at r.t. for 16 h. The reaction mixture was then evaporated under reduced pressure and purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) to provide the title compound as a white amorphous solid (12.2 mg, 0.037 mmol, 99%, 95% *ee*), m.p. 131-133 °C. Data are consistent with a reported example.[220]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.1 Hz, 2 H, H10), 7.24 (d, *J* = 8.4 Hz, 2 H, H2), 7.21 (d, *J* = 8.1 Hz, 2 H, H11), 7.18 (d, *J* = 8.4 Hz, 2 H, H3), 5.81 (dq, *J* = 6.3, 2.0 Hz, 1 H, H6), 5.61 (dq, *J* = 6.3, 2.3 Hz, 1 H, H7), 5.50 – 5.46 (m, 1 H, H5), 4.34 (ddd, *J* = 14.6, 4.7, 2.3 Hz, 1 H, H8a), 4.26 – 4.23 (m, 1 H, H8b), 2.40 (s, 3 H, H13).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.5 (C12), 139.2 (C4), 135.5 (C9), 133.8 (C1), 130.3 (C7), 129.7 (C11), 128.8 (C3), 128.7 (C2), 127.4 (C10), 125.1 (C6), 69.7 (C5), 55.6 (C8), 21.6 (C13).

FTIR (ν_{max}, cm^{-1}): 2921 (w), 1597 (w), 1491 (w), 1411 (w), 1346 (m), 1305 (w), 1162 (s), 1089 (m), 1059 (w), 1015 (w), 815 (m).

HRMS (ESI): calculated for $C_{17}H_{17}NO_2SCl$ $[M+H]^+$ 334.0663, found 334.0674.

R_f = 0.30 (20% EtOAc/hexane).

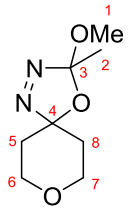
$[\alpha]_D^{25.0}$ = -268.2 ($CHCl_3$, *c* = 0.5, 95% *ee*); lit.[220] $[\alpha]_D^{20}$ = +215.2 ($CHCl_3$, *c* = 0.955, for opposite enantiomer; *ee* not stated, but at most 91% *ee*).

HPLC: ChiralART SC, 90:10 hexane/isopropanol, 1.0 mL/min flow rate, T = 25 °C, λ_{max} = 210 nm; t_R (min) = 33.7 (minor), 36.7 (major).

5.4. Experimental data for Chapter 4

5.4.1. Synthetic procedures and characterisation for oxadiazolines

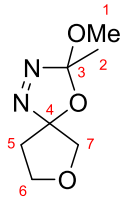
General procedure for oxadiazoline synthesis: A solution of the appropriate ketone (20.0 mmol, 1 equiv.) and acetic hydrazide (1.63 g, 22.0 mmol, 1.1 equiv.) in toluene (60 mL) was heated under reflux with equipped Dean-Stark apparatus for 2 h. The mixture was then evaporated under reduced pressure and the residue redissolved in MeOH (60 mL) and cooled to 0 °C. (Diacetoxyiodo)benzene (7.09 g, 22.0 mmol, 1.1 equiv.) was added portionwise, then the mixture stirred further at this temperature for 1 h. The mixture was evaporated under reduced pressure and the residue purified by silica gel column chromatography.



303

3-Methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (303): Following the general procedure for oxadiazoline synthesis using tetrahydro-4*H*-pyran-4-one (4.00 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as a colourless oil (6.39 g, 34.3 mmol, 86%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.12 – 4.06 (m, 1 H, H6/H7), 4.06 – 4.00 (m, 1 H, H6/H7), 3.91 – 3.83 (m, 2 H, H6/H7), 3.13 (s, 3 H, H1), 2.26 – 2.18 (m, 1 H, H5/H8), 2.08 – 2.01 (m, 1 H, H5/H8), 1.79 – 1.72 (m, 1 H, H5/H8), 1.66 (s, 3 H, H2), 1.61 – 1.54 (m, 1 H, H5/H8).
^{13}C NMR (150 MHz, $CDCl_3$): δ 133.2 (C3), 118.8 (C4), 65.1 (C6 and C7), 50.7 (C1), 35.2 (C5/C8), 34.1 (C5/C8), 23.9 (C2).
FTIR (ν_{max}, cm^{-1}): 2963 (w), 2865 (w), 1739 (w), 1575 (w), 1470 (w), 1436 (w), 1378 (m), 1350 (w), 1304 (w), 1234 (m), 1200 (s), 1152 (s), 1119 (m), 1098 (s), 1054 (s), 1029 (m), 1019 (m), 1008 (m), 990 (m), 941 (m), 906 (s), 868 (s), 842 (w), 807 (w), 770 (w).
HRMS (ESI): calculated for $C_8H_{15}N_2O_3$ $[M+H]^+$ 187.1077, found 187.1070.
R_f = 0.13 (10% EtOAc/hexane).



304

3-Methoxy-3-methyl-4,7-dioxa-1,2-diazaspiro[4.4]non-1-ene (304): Following the general procedure for oxadiazoline synthesis using tetrahydrofuran-3-one (3.44 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a colourless oil (4.90 g, 28.5 mmol, 71%).

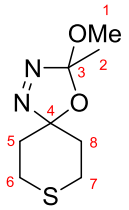
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.25 – 4.17 (m, 1.5 H, H6a of diastereomers A and B, H7a of diastereomer A), 4.12 (dt, *J* = 8.8, 7.2 Hz, 0.5 H, H6b of diastereomer B), 4.10 – 4.04 (m, 0.5 H, H6b of diastereomer A), 4.00 (d, *J* = 10.0 Hz, 0.5 H, H7a of diastereomer B), 3.76 (d, *J* = 10.3 Hz, 0.5 H, H7b of diastereomer A), 3.64 (d, *J* = 10.0 Hz, 0.5 H, H7b of diastereomer B), 3.08 and 3.03 (two s, 3 H, H1), 2.65 – 2.57 (m, 0.5 H, H5a of diastereomer B), 2.43 (dt, *J* = 13.2, 7.7 Hz, 0.5 H, H5a of diastereomer A), 2.17 (ddd, *J* = 13.3, 7.2, 6.1 Hz, 0.5 H, H5b of diastereomer B), 2.03 – 1.97 (m, 0.5 H, H5b of diastereomer A), 1.63 and 1.59 (two s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 134.4 and 134.2 (C3), 126.7 and 126.6 (C4), 73.4 and 73.1 (C7), 68.9 and 68.8 (C6), 50.5 and 50.2 (C1), 36.8 and 36.2 (C5), 22.9 and 22.6 (C2).

FTIR (ν_{max}, cm^{-1}): 2993 (w), 2947 (w), 2867 (w), 1571 (w), 1459 (w), 1435 (w), 1380 (m), 1334 (w), 1206 (s), 1148 (s), 1105 (m), 1051 (s), 965 (w), 911 (s), 869 (m), 764 (w).

HRMS (ESI): calculated for $C_7H_{13}N_2O_3$ $[M+H]^+$ 173.0921, found 173.0928.

***R*$_f$** = 0.23 (10% EtOAc/hexane).

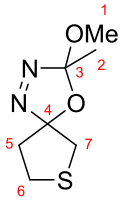


305

3-Methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (305): Following the general procedure for oxadiazoline synthesis using tetrahydro-4*H*-thiopyran-4-one (2.32 g,

20.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as a colourless oil (3.15 g, 15.6 mmol, 78%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.14 (s, 3 H, H1), 2.95 – 2.79 (m, 4 H, H6 and H7), 2.41 (ddd, *J* = 13.8, 10.0, 4.0 Hz, 1 H, H5/H8), 2.26 (ddd, *J* = 13.8, 10.4, 3.6 Hz, 1 H, H5/H8), 1.94 – 1.88 (m, 1 H, H5/H8), 1.69 (ddd, *J* = 13.8, 6.1, 2.8 Hz, 1 H, H5/H8), 1.66 (s, 3 H, H2).
^{13}C NMR (150 MHz, $CDCl_3$): δ 133.5 (C3), 120.2 (C4), 50.8 (C1), 35.8 (C5/C8), 34.8 (C5/C8), 25.4 (C6/C7), 25.3 (C6/C7), 23.9 (C2).
FTIR (ν_{max}, cm^{-1}): 2998 (w), 2947 (w), 2920 (w), 2836 (w), 1574 (w), 1430 (m), 1377 (m), 1353 (w), 1321 (w), 1275 (w), 1226 (m), 1200 (s), 1156 (s), 1093 (m), 1083 (s), 1048 (s), 1010 (w), 986 (w), 946 (s), 901 (s), 850 (m), 786 (w), 767 (w).
HRMS (ESI): calculated for $C_8H_{15}N_2O_2S$ $[M+H]^+$ 203.0849, found 203.0851.
***R*$_f$** = 0.39 (10% EtOAc/hexane).



306

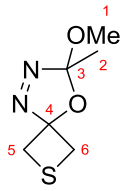
3-Methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (306): Following the general procedure for oxadiazoline synthesis using 4,5-dihydro-3(2*H*)-thiophenone (2.04 g, 20.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a pale yellow oil (2.30 g, 12.2 mmol, 61%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.44 (d, *J* = 12.0 Hz, 0.5 H, H7a of diastereomer A), 3.27 (d, *J* = 11.8 Hz, 0.5 H, H7a of diastereomer B), 3.23 – 3.14 (m, 1 H, H6a of diastereomers A and B), 3.12 and 3.11 (two s, 3 H, H1), 3.11 – 3.06 (m, 1 H, H6b of diastereomers A and B), 2.94 (dd, *J* = 12.0, 0.9 Hz, 0.5 H, H7b of diastereomer A), 2.75 (dd, *J* = 11.8, 0.9 Hz, 0.5 H, H7b of diastereomer B), 2.59 (dt, *J* = 13.2, 7.7 Hz, 0.5 H, H5a of diastereomer A), 2.44 – 2.36 (m, 0.5 H, H5a of diastereomer B), 2.28 – 2.20 (m, 0.5 H, H5b of diastereomer A), 2.09 – 2.03 (m, 0.5 H, H5b of diastereomer B), 1.643 and 1.642 (two s, 3 H, H2).
^{13}C NMR (150 MHz, $CDCl_3$): δ 134.6 and 134.5 (C3), 128.45 and 128.39 (C4), 50.73 and 50.69 (C1), 39.8 and 39.0 (C5), 37.6 and 36.8 (C7), 29.49 and 29.48 (C6), 23.1 and 22.9 (C2).

FTIR (ν_{max}, cm^{-1}): 2972 (w), 2941 (w), 1738 (w), 1570 (w), 1456 (w), 1435 (w), 1378 (m), 1315 (w), 1225 (m), 1204 (s), 1153 (s), 1124 (m), 1088 (m), 1051 (s), 1017 (w), 977 (w), 947 (m), 908 (s), 866 (m), 834 (w), 770 (w).

HRMS (ESI): calculated for $C_7H_{13}N_2O_2S$ $[M+H]^+$ 189.0692, found 189.0690.

R_f = 0.37 (10% EtOAc/hexane).



307

7-Methoxy-7-methyl-8-oxa-2-thia-5,6-diazaspiro[3.4]oct-5-ene (307): Following the general procedure for oxadiazoline synthesis using 3-thietanone (0.97 g, 11.0 mmol), purified by silica gel column chromatography (eluent: hexane → 40% CH_2Cl_2/hexane) provided the title compound as a pale yellow oil (0.57 g, 3.26 mmol, 30%).

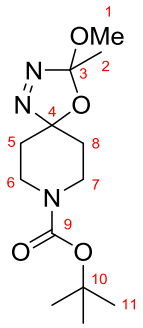
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.84 (d, *J* = 10.2 Hz, 1 H, H5a), 3.77 (d, *J* = 10.2 Hz, 1 H, H6a), 3.45 (dd, *J* = 10.2, 1.8 Hz, 1 H, H5b), 3.29 (dd, *J* = 10.2, 1.8 Hz, 1 H, H6b), 2.92 (s, 3 H, H1), 1.57 (s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 136.1 (C3), 117.8 (C4), 50.2 (C1), 37.3 (C5/C6), 37.1 (C5/C6), 23.3 (C2).

FTIR (ν_{max}, cm^{-1}): 2999 (w), 2942 (w), 2837 (w), 1568 (w), 1459 (w), 1437 (w), 1418 (w), 1380 (m), 1237 (m), 1204 (s), 1174 (m), 1158 (m), 1134 (m), 1097 (s), 1049 (s), 959 (w), 909 (s), 862 (m), 776 (w).

HRMS (ESI): calculated for $C_6H_{11}N_2O_2S$ $[M+H]^+$ 175.0536, found 175.0540.

R_f = 0.29 (40% CH_2Cl_2/hexane).



308

***tert*-Butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (308):** Following the general procedure for oxadiazoline synthesis using *N*-Boc-4-piperidone (4.28 g, 25.0 mmol), purified by silica gel column chromatography (eluent: hexane → 20% EtOAc/hexane) provided the title compound as a white amorphous solid (5.43 g, 19.0 mmol, 76%), m.p. 60-62 °C.

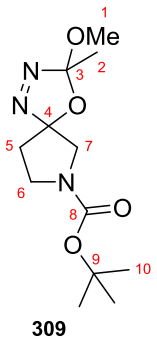
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.02 – 3.79 (m, 2 H, H6/H7), 3.51 – 3.41 (m, 2 H, H6/H7), 3.14 (s, 3 H, H1), 2.19 – 2.09 (m, 1 H, H5/H8), 2.04 – 1.92 (m, 1 H, H5/H8), 1.73 – 1.62 (m, 1 H, H5/H8), 1.66 (s, 3 H, H2), 1.52 – 1.46 (m, 1 H, H5/H8), 1.48 (s, 9 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.7 (C9), 133.4 (C3), 119.7 (C4), 80.2 (C10), 50.8 (C1), 41.8 – 41.1 (br, C6/C7), 41.1 – 40.5 (br, C6/C7), 34.4 – 34.3 (br, C5/C8), 33.4 – 33.2 (br, C5/C8), 28.6 (C11), 23.8 (C2).

FTIR (ν_{max}, cm^{-1}): 2973 (w), 1693 (s, C=O), 1574 (w), 1468 (w), 1418 (m), 1378 (w), 1366 (m), 1351 (w), 1278 (w), 1246 (m), 1223 (m), 1202 (m), 1154 (s), 1097 (s), 1055 (s), 1003 (w), 966 (w), 933 (m), 906 (s), 867 (m), 825 (w), 804 (w), 769 (w).

HRMS (ESI): calculated for $C_{13}H_{23}N_3O_4Na$ $[M+Na]^+$ 308.1581, found 308.1590.

***R*$_f$** = 0.37 (20% EtOAc/hexane).

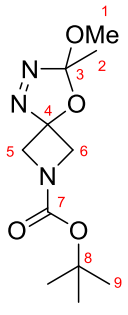


309

***tert*-Butyl 3-methoxy-3-methyl-4-oxa-1,2,7-triazaspiro[4.4]non-1-ene-7-carboxylate (309):** Following the general procedure for oxadiazoline synthesis using *N*-Boc-3-

pyrrolidinone (3.70 g, 20.0 mmol), purified by silica gel column chromatography (eluent: hexane → 20% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a yellow oil (4.19 g, 15.4 mmol, 77%).

^{1}H NMR (600 MHz, MeOD-*d*$_4$): δ 3.82 (d, *J* = 12.2 Hz, 0.5 H, H7a of diastereomer A), 3.79 – 3.60 (m, 2.5 H, H6 of diastereomers A and B, H7a of diastereomer B), 3.49 (d, *J* = 12.2 Hz, 0.5 H, H7b of diastereomer A), 3.40 – 3.32 (m, 0.5 H, H7b of diastereomer B), 3.07 and 3.04 (two s, 3 H, H1), 2.47 (m, 0.5 H, H5a of diastereomer A), 2.33 – 2.20 (m, 1 H, H5b of diastereomer A, H5a of diastereomer B), 2.18 – 2.08 (m, 0.5 H, H5b of diastereomer B), 1.60 and 1.58 (two s, 3 H, H2), 1.50 (br s, 9 H, H10).
^{13}C NMR (150 MHz, MeOD-*d*$_4$): δ 154.5 (C8), 134.6 and 134.3 (C3), 124.1 and 124.00 and 123.3 (rotameric, C4), 80.1 (C9), 52.0 and 51.7 and 51.5 and 51.2 (rotameric, C7), 49.6 and 49.3 (C1), 44.8 and 44.7 and 44.3 and 44.2 (rotameric, C6), 34.3 and 33.55 and 33.51 and 32.8 (rotameric, C5), 27.4 (C10), 21.7 (C2).
FTIR (ν_{max}, cm^{-1}): 2976 (w), 2889 (w), 1740 (w), 1696 (s, C=O), 1479 (w), 1457 (w), 1399 (s), 1366 (m), 1236 (m), 1207 (m), 1145 (s), 1095 (s), 1052 (s), 995 (w), 913 (s), 880 (m), 868 (m), 771 (m).
HRMS (ESI): calculated for $C_{12}H_{21}N_3O_4Na$ $[M+Na]^+$ 294.1424, found 294.1421.
***R*$_f$** = 0.36 (20% EtOAc/hexane).



310

***tert*-Butyl 7-methoxy-7-methyl-8-oxa-2,5,6-triazaspiro[3.4]oct-5-ene-2-carboxylate (310):** Following the general procedure for oxadiazoline synthesis using *N*-Boc-3-azetidinone (2.57 g, 15.0 mmol), purified by silica gel column chromatography (eluent: 10% → 20% EtOAc/hexane) provided the title compound as a white amorphous solid (0.98 g, 3.81 mmol, 25%), m.p. 64-66 °C.

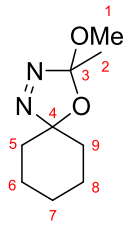
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.49 (dd, *J* = 9.8, 1.1 Hz, 1 H, H5a), 4.38 (dd, *J* = 9.7, 1.1 Hz, 1 H, H6a), 4.20 (dd, *J* = 9.8, 0.9 Hz, 1 H, H5b), 4.14 (dd, *J* = 9.7, 0.9 Hz, 1 H, H6b), 2.93 (s, 3 H, H1), 1.62 (s, 3 H, H2), 1.47 (s, 9 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.0 (C7), 135.8 (C3), 111.7 (C4), 80.7 (C8), 59.4 – 58.0 (br, C5 and C6), 50.1 (C1), 28.4 (C9), 22.7 (C2).

FTIR (ν_{max}, cm^{-1}): 2976 (w), 2946 (w), 1706 (s, C=O), 1564 (w), 1457 (w), 1392 (s), 1382 (s), 1368 (s), 1322 (w), 1248 (m), 1204 (m), 1157 (m), 1098 (s), 1059 (s), 910 (m), 865 (m), 806 (w), 772 (w).

HRMS (ESI): calculated for $C_{11}H_{19}N_3O_4Na$ $[M+Na]^+$ 280.1268, found 280.1265.

***R*$_f$** = 0.44 (20% EtOAc/hexane).



311

3-Methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.5]dec-1-ene (311): Following the general procedure for oxadiazoline synthesis using cyclohexanone (3.93 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 5% EtOAc/hexane) provided the title compound as a colourless oil (5.89 g, 32.0 mmol, 80%). Data are consistent with a reported example.[39]

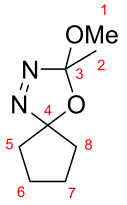
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.11 (s, 3 H, H1), 2.10 – 2.01 (m, 1 H, H5/H9), 1.95 – 1.80 (m, 3 H, H5/H9 and H6/H7/H8), 1.73 – 1.60 (m, 4 H, H5/H9 and H6/H7/H8), 1.64 (s, 3 H, H2), 1.58 – 1.50 (m, 1 H, H6/H7/H8), 1.47 – 1.39 (m, 1 H, H5/H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 132.5 (C3), 122.0 (C4), 50.6 (C1), 34.9 (C5/C9), 33.6 (C5/C9), 25.0 (C6/C7/C8), 24.2 (C2), 23.1 (C6/C7/C8), 22.9 (C6/C7/C8).

FTIR (ν_{max}, cm^{-1}): 2999 (w), 2940 (m), 2864 (w), 1572 (w), 1450 (m), 1376 (m), 1345 (w), 1233 (m), 1198 (s), 1156 (m), 1127 (m), 1092 (m), 1083 (m), 1056 (s), 1037 (w), 982 (m), 920 (m), 904 (s), 868 (m), 831 (w), 817 (w), 766 (w).

HRMS (ESI): calculated for $C_9H_{17}N_2O_2$ $[M+H]^+$ 185.1285, found 185.1289.

***R*$_f$** = 0.35 (5% EtOAc/hexane).



312

3-Methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.4]non-1-ene (312): Following the general procedure for oxadiazoline synthesis using cyclopentanone (3.36 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 5% EtOAc/hexane) provided the title compound as a colourless oil (6.41 g, 37.7 mmol, 94%). Data are consistent with a reported example.[39]

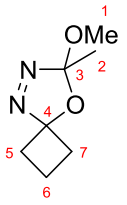
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.01 (s, 3 H, H1), 2.29 – 2.20 (m, 1 H, H5/H8), 2.05 – 1.97 (m, 1 H, H5/H8), 1.97 – 1.81 (m, 5 H, H6 and H7, H5/H8), 1.72 – 1.64 (m, 1 H, H5/H8), 1.55 (s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.1 (C3), 128.8 (C4), 50.2 (C1), 36.5 (C5/C8), 35.6 (C5/C8), 25.4 (C6/C7), 25.2 (C6/C7), 23.1 (C2).

FTIR (ν_{max}, cm^{-1}): 2966 (w), 2878 (w), 2837 (w), 1570 (w), 1455 (w), 1435 (w), 1377 (m), 1329 (w), 1238 (m), 1201 (s), 1155 (s), 1132 (m), 1095 (m), 1055 (s), 1018 (w), 973 (w), 950 (w), 911 (s), 870 (m), 760 (w).

HRMS (ESI): calculated for $C_8H_{15}N_2O_2$ $[M+H]^+$ 171.1128, found 171.1128.

R_f = 0.33 (5% EtOAc/hexane).



313

7-Methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (313): Following the general procedure for oxadiazoline synthesis using cyclobutanone (2.80 g, 40.0 mmol), purified by silica gel column chromatography (eluent: pentane → 20% Et_2O/pentane) provided the title compound as a volatile colourless oil (3.01 g, 19.3 mmol, 48%).

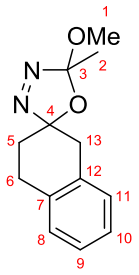
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.93 (s, 3 H, H1), 2.59 – 2.49 (m, 3 H, H5/H7), 2.44 – 2.37 (m, 1 H, H5/H7), 2.28 – 2.17 (m, 1 H, H6a), 1.98 – 1.88 (m, 1 H, H6b), 1.59 (s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.7 (C3), 119.0 (C4), 50.0 (C1), 33.6 (C5/C7), 33.5 (C5/C7), 23.3 (C2), 11.9 (C6).

FTIR (ν_{max}, cm^{-1}): 2999 (w), 2945 (w), 2837 (w), 1563 (w), 1460 (w), 1438 (w), 1419 (w), 1379 (m), 1275 (m), 1246 (m), 1204 (s), 1182 (s), 1148 (s), 1110 (m), 1066 (s), 1052 (s), 959 (m), 910 (s), 869 (m), 821 (w), 768 (w).

HRMS (ESI): calculated for $C_7H_{13}N_2O_2$ $[M+H]^+$ 157.0972, found 157.0974.

***R*$_f$** = 0.73 (30% EtOAc/hexane).



314

5'-Methoxy-5'-methyl-3,4-dihydro-1*H*,5'*H*-spiro[naphthalene-2,2'-[1,3,4]oxadiazole] (314): Following the general procedure for oxadiazoline synthesis using 2-tetralone (6.50 g, 44.5 mmol), purified by silica gel column chromatography (eluent: hexane → 5% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a red viscous oil (9.01 g, 38.8 mmol, 87%).

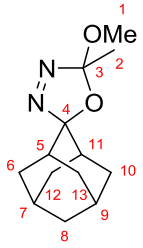
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 – 7.15 (m, 3 H, H8, H9 and H10), 7.13 – 7.05 (m, 1 H, H11), 3.48 (d, *J* = 16.9 Hz, 0.5 H, H13a of diastereomer A), 3.35 (d, *J* = 16.7 Hz, 0.5 H, H13a of diastereomer B), 3.19 and 3.18 (two s, 3 H, H1), 3.17 – 3.02 (m, 2 H, H6), 2.96 (d, *J* = 16.9 Hz, 0.5 H, H13b of diastereomer A), 2.73 (d, *J* = 16.7 Hz, 0.5 H, H13b of diastereomer B), 2.42 (ddd, *J* = 13.4, 9.5, 6.1 Hz, 0.5 H, H5a of diastereomer B), 2.27 – 2.20 (m, 0.5 H, H5a of diastereomer A), 2.03 – 1.96 (m, 0.5 H, H5b of diastereomer B), 1.86 – 1.79 (m, 0.5 H, H5b of diastereomer A), 1.71 and 1.70 (two s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.08 and 135.05 (C7), 133.59 and 133.57 (C3), 132.5 (C12), 129.1 (C11), 128.77 and 128.76 (C8), 126.67 and 126.65 (C9), 126.46 and 126.44 (C10), 120.8 and 120.7 (C4), 50.7 (C1), 37.8 and 36.9 (C13), 31.9 and 30.7 (C6), 27.0 and 26.7 (C5), 23.91 and 23.88 (C2).

FTIR (ν_{max}, cm^{-1}): 3000 (w), 2941 (w), 2836 (w), 1573 (w), 1497 (w), 1454 (w), 1435 (w), 1377 (m), 1344 (w), 1299 (w), 1227 (m), 1200 (s), 1156 (s), 1136 (m), 1118 (m), 1089 (m), 1050 (s), 1003 (w), 968 (m), 906 (s), 869 (m), 849 (w), 832 (w), 775 (w).

HRMS (ESI): calculated for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1293.

R_f = 0.27 (5% EtOAc/hexane).



315

5'-Methoxy-5'-methyl-5'*H*-spiro[adamantane-2,2'-[1,3,4]oxadiazole] (315): Following the general procedure for oxadiazoline synthesis using 2-adamantanone (6.01 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as a white crystalline solid (7.55 g, 31.9 mmol, 80%), m.p. 70-72 °C (lit. m.p.[221] 72 °C). Data are consistent with a reported example.[221]

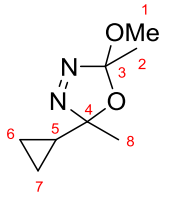
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.07 (s, 3 H, H1), 2.65 – 2.60 (m, 1 H, H6/H10/H12/H13), 2.48 – 2.43 (m, 1 H, H6/H10/H12/H13), 2.10 – 2.04 (m, 2 H, H7/H9, H6/H10/H12/H13), 2.04 – 1.99 (m, 1 H, H6/H10/H12/H13), 1.92 – 1.86 (m, 2 H, H6/H10/H12/H13), 1.85 – 1.76 (m, 4 H, H5/H11, H7/H9, H8), 1.76 – 1.68 (m, 2 H, H6/H10/H12/H13), 1.61 (s, 3 H, H2), 1.55 – 1.51 (m, 1 H, H5/H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 131.7 (C3), 125.3 (C4), 50.3 (C1), 38.3 (C5/C11), 37.3 (C8), 36.5 (C5/C11), 35.2 (C6/C10/C12/C13), 35.1 (C6/C10/C12/C13), 34.5 (C6/C10/C12/C13), 34.1 (C6/C10/C12/C13), 27.4 (C7/C9), 26.7 (C7/C9), 24.4 (C2).

FTIR (ν_{max}, cm^{-1}): 2998 (w), 2937 (m), 2908 (s), 2854 (m), 1575 (w), 1468 (w), 1451 (m), 1433 (w), 1375 (m), 1363 (w), 1351 (w), 1280 (w), 1247 (m), 1222 (m), 1196 (s), 1155 (m), 1109 (s), 1092 (m), 1059 (s), 1022 (m), 999 (w), 948 (w), 911 (s), 880 (m), 859 (m), 839 (w), 801 (w), 779 (w), 764 (w).

HRMS (ESI): calculated for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237.1598, found 237.1590.

R_f = 0.48 (10% EtOAc/hexane).



316

2-Cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (316): Following the general procedure for oxadiazoline synthesis using cyclopropyl methyl ketone (3.36 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a colourless oil (4.74 g, 27.8 mmol, 70%). Compound has been prepared previously,[39] but NMR spectra were recorded in C_6D_6.

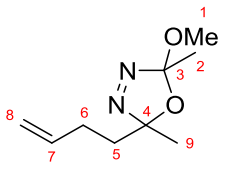
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.27 and 3.17 (two s, 3 H, H1), 1.68 and 1.62 (two s, 3 H, H2), 1.58 and 1.40 (two s, 3 H, H8), 1.33 – 1.23 (m, 1 H, H5), 0.73 – 0.66 (m, 0.5 H, H6/H7), 0.63 – 0.46 (m, 3 H, H6/H7), 0.38 – 0.32 (m, 0.5 H, H6/H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.3 and 133.1 (C3), 122.2 and 122.1 (C4), 51.1 and 50.8 (C1), 23.0 and 22.66 (C2), 22.70 and 22.66 (C8), 18.3 and 17.5 (C5), 2.4 and 1.5 (C6/C7), 1.7 and 1.6 (C6/C7).

FTIR (ν_{max}, cm^{-1}): 2998 (w), 2945 (w), 2837 (w), 1575 (w), 1456 (w), 1376 (m), 1230 (m), 1195 (m), 1144 (s), 1105 (m), 1055 (s), 1027 (m), 968 (m), 930 (m), 908 (m), 885 (m), 870 (m), 840 (w), 822 (w), 786 (w), 757 (w).

HRMS (ESI): calculated for $C_8H_{15}N_2O_2$ $[M+H]^+$ 171.1128, found 171.1130.

***R*$_f$** = 0.54 (10% EtOAc/hexane).



317

2-(But-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (317): Following the general procedure for oxadiazoline synthesis using 5-hexen-2-one (3.93 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1.5:1) as a colourless oil (4.92 g, 26.7 mmol, 67%).

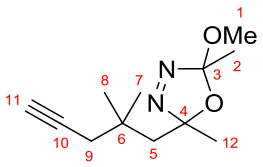
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.89 – 5.73 (m, 1 H, H7), 5.08 – 4.95 (m, 2 H, H8), 3.17 and 3.16 (two s, 3 H, H1), 2.39 – 2.29 (m, 0.4 H, H6a of diastereomer A), 2.28 – 2.12 (m, 1 H, H6b of diastereomer A, H6a of diastereomer B), 2.11 – 2.00 (m, 1 H, H5a of diastereomer A, H6b of diastereomer B), 1.93 (ddd, *J* = 13.9, 11.5, 5.1 Hz, 0.6 H, H5a of diastereomer B), 1.79 – 1.70 (m, 1 H, H5b of diastereomers A and B), 1.66 and 1.63 (two s, 3 H, H2), 1.55 and 1.44 (two s, 3 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 137.5 and 137.3 (C7), 133.4 and 133.2 (C3), 122.3 and 122.1 (C4), 115.34 and 115.30 (C8), 50.80 and 50.75 (C1), 37.6 and 36.8 (C5), 28.2 and 28.0 (C6), 23.4 and 22.6 (C2), 22.5 and 22.4 (C9).

FTIR (ν_{max}, cm^{-1}): 2999 (w), 2946 (w), 1643 (w), 1574 (w), 1455 (w), 1376 (m), 1226 (m), 1190 (m), 1150 (s), 1055 (m), 978 (w), 907 (s), 869 (m).

HRMS (ESI): calculated for $C_9H_{17}N_2O_2$ $[M+H]^+$ 185.1285, found 185.1280.

***R*$_f$** = 0.33 (5% EtOAc/hexane).



318

2-(2,2-Dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (318): Following the general procedure for oxadiazoline synthesis using 4,4-dimethylhept-6-yn-2-one (1.38 g, 10.0 mmol), purified by silica gel column chromatography (eluent: hexane → 5% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1:1) as a colourless oil (1.82 g, 8.1 mmol, 81%).

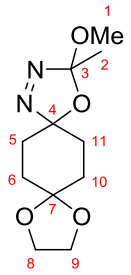
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.18 and 3.15 (two s, 3 H, H1), 2.30 – 2.16 (m, 2.5 H, H5a of diastereomer A and H9), 2.05 (d, *J* = 14.8 Hz, 0.5 H, H5a of diastereomer B), 1.99 (t, *J* = 2.6 Hz, 1 H, H11), 1.67 and 1.61 (two s, 3 H, H2), 1.66 (d, *J* = 14.8 Hz, 0.5 H, H5b of diastereomer A), 1.59 and 1.47 (two s, 3 H, H12), 1.54 (d, *J* = 14.8 Hz, 0.5 H, H5b of diastereomer B), 1.17 and 1.16 (two s, 3 H, H7/H8), 1.114 and 1.107 (two s, 3 H, H7/H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 134.3 and 133.8 (C3), 122.6 and 122.4 (C4), 82.2 and 82.1 (C10), 70.85 and 70.83 (C11), 51.1 and 50.7 (C1), 47.1 and 46.8 (C5), 33.9 and 33.8 (C6), 33.7 and 33.4 (C9), 28.6 and 28.5 (C7/C8), 28.4 and 28.3 (C7/C8), 24.4 and 24.1 (C12), 23.5 and 22.8 (C2).

FTIR (ν_{max}, cm^{-1}): 3296 (w, alkyne CH), 2964 (m), 2838 (w), 1718 (w), 1577 (w), 1456 (m), 1376 (m), 1195 (s), 1153 (s), 1081 (m), 1056 (s), 1020 (w), 995 (w), 959 (m), 914 (m), 882 (m), 858 (m), 763 (w).

HRMS (ESI): calculated for $C_{12}H_{21}N_2O_2$ $[M+H]^+$ 225.1598, found 225.1602.

R_f = 0.22 (5% EtOAc/hexane).



319

3-Methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (319): Following the general procedure for oxadiazoline synthesis using 1,4-cyclohexanedione monoethylene acetal (3.12 g, 20.0 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a white crystalline solid (3.94 g, 16.3 mmol, 81%), m.p. 57-58 °C.

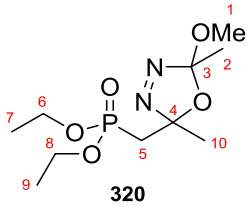
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.98 (s, 4 H, H8 and H9), 3.11 (s, 3 H, H1), 2.34 – 2.26 (m, 1 H, H5/H6/H10/H11), 2.18 – 2.11 (m, 1 H, H5/H6/H10/H11), 2.04 – 1.92 (m, 2 H, H5/H6/H10/H11), 1.91 – 1.84 (m, 2 H, H5/H6/H10/H11), 1.80 – 1.74 (m, 1 H, H5/H6/H10/H11), 1.63 (s, 3 H, H2), 1.59 – 1.52 (m, 1 H, H5/H6/H10/H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.0 (C3), 120.8 (C4), 107.6 (C7), 64.7 (C8/C9), 64.6 (C8/C9), 50.6 (C1), 32.4 (C5/C6/C10/C11), 31.7 (C5/C6/C10/C11), 31.6 (C5/C6/C10/C11), 31.2 (C5/C6/C10/C11), 23.9 (C2).

FTIR (ν_{max}, cm^{-1}): 2941 (w), 2888 (w), 1572 (w), 1439 (w), 1375 (m), 1337 (w), 1299 (w), 1263 (w), 1233 (m), 1200 (m), 1169 (m), 1158 (m), 1107 (s), 1074 (w), 1055 (m), 1034 (s), 995 (m), 968 (m), 947 (m), 921 (m), 906 (s), 864 (w), 854 (w), 766 (w).

HRMS (ESI): calculated for $C_{11}H_{19}N_2O_4$ $[M+H]^+$ 243.1339, found 243.1329.

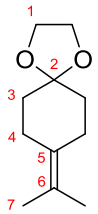
R_f = 0.31 (20% EtOAc/hexane).



320

Diethyl ((5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)phosphonate (320): Following the general procedure for oxadiazoline synthesis using diethyl (2-oxopropyl)phosphonate (3.88 g, 20.0 mmol), purified by silica gel column chromatography (eluent: hexane → 60% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1.5:1) as a pale yellow oil (3.33 g, 11.9 mmol, 59%).

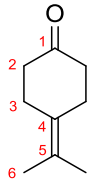
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.21 – 4.09 (m, 4 H, H6 and H8), 3.16 and 3.15 (two s, 3 H, H1), 2.55 (dd, *J* = 20.0, 15.3 Hz, 0.4 H, H5a of diastereomer A), 2.42 (dd, *J* = 19.4, 15.5 Hz, 0.6 H, H5a of diastereomer B), 2.09 (dd, *J* = 19.2, 15.3 Hz, 0.4 H, H5b of diastereomer A), 1.97 (dd, *J* = 19.1, 15.5 Hz, 0.6 H, H5b of diastereomer B), 1.77 and 1.669 (two s, 3 H, H10), 1.673 and 1.65 (s, 3 H, H2), 1.36 – 1.30 (m, 6 H, H7 and H9).
^{13}C NMR (150 MHz, $CDCl_3$): δ 135.2 and 135.1 (C3), 118.7 and 118.5 (d, *J* = 2.9 Hz; d, *J* = 2.3 Hz, C4), 62.42 and 62.26 (d, *J* = 6.3 Hz; d, *J* = 6.4 Hz, C6/C8), 62.15 and 62.11 (d, *J* = 6.4 Hz; d, *J* = 6.4 Hz, C6/C8), 50.9 and 50.8 (C1), 35.3 and 34.7 (d, *J* = 142.5 Hz; d, *J* = 142.6 Hz, C5), 23.8 and 22.9 (C2), 23.43 and 23.42 (d, *J* = 4.3 Hz; d, *J* = 2.0 Hz, C10), 16.54 and 16.50 (d, *J* = 6.4 Hz; d, *J* = 6.4 Hz, C7 and C9).
^{31}P NMR (245 MHz, $CDCl_3$): δ 23.4 and 23.2 (two s, 1 P, C5-P).
FTIR (ν_{max}, cm^{-1}): 2987 (w), 1740 (w), 1576 (w), 1444 (w), 1379 (w), 1243 (m), 1202 (m), 1157 (m), 1098 (w), 1049 (s), 1020 (s), 958 (s), 912 (m), 881 (w), 835 (w), 795 (m).
HRMS (ESI): calculated for $C_{10}H_{22}N_2O_5P$ $[M+H]^+$ 281.1261, found 281.1265.
R_f = 0.20 (60% EtOAc/hexane).



8-(Propan-2-ylidene)-1,4-dioxaspiro[4.5]decane: To a suspension of isopropyltriphenylphosphonium bromide (9.40 g, 24.4 mmol, 1 equiv.) and sodium hydride (1.17 g, 29.3 mmol, 1.2 equiv., 60% dispersion in mineral oil) in anhydrous DMSO (15 mL)

was heated at 50 °C until formation of a red solution. A solution of 1,4-cyclohexanedione monoethylene acetal (3.81 g, 24.4 mmol) in anhydrous DMSO (15 mL) was then added to the reaction mixture and stirred further at 50 °C for 16 h. The mixture was cooled to r.t., quenched with water (15 mL) then extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), evaporated under reduced pressure and purified by silica gel column chromatography (eluent: 5% EtOAc/hexane) to provide the title compound as a colourless oil (1.57 g, 8.6 mmol, 35%). Data are consistent with a reported example.[222]

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.95 (s, 4 H, H1), 2.32 – 2.25 (m, 4 H, H4), 1.67 (s, 6 H, H7), 1.65 – 1.61 (m, 4 H, H3).
^{13}C NMR (150 MHz, $CDCl_3$): δ 129.4 (C5), 122.0 (C6), 109.2 (C2), 64.4 (C1), 35.8 (C3), 26.9 (C4), 20.3 (C7).
FTIR (ν_{max}, cm^{-1}): 2994 (m), 2877 (m), 1445 (w), 1364 (w), 1343 (w), 1280 (w), 1233 (w), 1136 (m), 1109 (s), 1070 (m), 1036 (m), 995 (w), 944 (m), 909 (m), 865 (w), 770 (w).
HRMS (ESI): calculated for $C_{11}H_{19}O_2$ $[M+H]^+$ 183.1380, found 183.1381.
R_f = 0.15 (5% EtOAc/hexane).



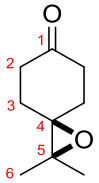
4-(Propan-2-ylidene)cyclohexan-1-one: To a suspension of silica gel (3.4 g) in CH_2Cl_2 (10 mL) was added 15% aqueous H_2SO_4 (0.6 mL) and stirred for 5 min. 8-(propan-2-ylidene)-1,4-dioxaspiro[4.5]decane (1.50 g, 8.23 mmol) was added and the mixture stirred at r.t. for 2 h. The silica was filtered off, washed with CH_2Cl_2 (25 mL) and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) to provide the title compound as a colourless oil (0.819 g, 5.93 mmol, 72%). Data are consistent with a reported example.[222]

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.58 – 2.49 (m, 4 H, H3), 2.43 – 2.36 (m, 4 H, H2), 1.71 (s, 6 H, H6).
^{13}C NMR (150 MHz, $CDCl_3$): δ 213.2 (C1), 126.3 (C4), 125.0 (C5), 40.5 (C2), 27.1 (C3), 20.4 (C6).

FTIR (ν_{max}, cm^{-1}): 2912 (w), 2858 (w), 1715 (s, C=O), 1442 (w), 1376 (w), 1342 (w), 1300 (w), 1233 (w), 1167 (w), 1129 (w), 946 (w), 909 (w), 811 (w), 765 (w).

HRMS (ESI): calculated for $C_9H_{15}O$ $[M+H]^+$ 139.1117, found 139.1115.

R_f = 0.33 (10% EtOAc/hexane).



2,2-Dimethyl-1-oxaspiro[2.5]octan-6-one: To a solution of 4-(propan-2-ylidene)cyclohexan-1-one (0.819 g, 5.93 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was added *m*-CPBA (2.25 g, 6.52 mmol, 50% purity) in three portions at 0 °C and the mixture warmed to r.t. and stirred further for 2 h. The mixture was filtered to remove precipitated *m*-chlorobenzoic acid, washed on the filter with CH_2Cl_2 (2 × 15 mL), then the filtrate washed with saturated aqueous Na_2CO_3 solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$), evaporated under reduced pressure and purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) to provide the title compound as a white amorphous solid (0.734 g, 4.76 mmol, 80%), m.p. 50-52 °C (lit. m.p.[223] 50-51 °C). Data are consistent with a reported example.[223]

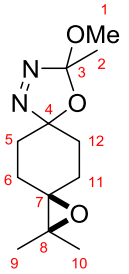
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.65 – 2.56 (m, 2 H, H2a), 2.44 – 2.36 (m, 2 H, H2b), 2.10 – 2.02 (m, 2 H, H3a), 1.99 – 1.91 (m, 2 H, H3b), 1.40 (s, 6 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ 210.7 (C1), 64.1 (C4), 63.4 (C5), 38.6 (C2), 29.3 (C3), 21.1 (C6).

FTIR (ν_{max}, cm^{-1}): 2965 (w), 2923 (w), 1717 (s, C=O), 1435 (w), 1378 (w), 1340 (w), 1308 (w), 1233 (w), 1124 (w), 1000 (w), 955 (w), 890 (w), 869 (w).

HRMS (ESI): calculated for $C_9H_{14}O_2Na$ $[M+Na]^+$ 177.0886, found 177.0893.

R_f = 0.31 (30% EtOAc/hexane).



321

9-Methoxy-2,2,9-trimethyl-1,10-dioxa-7,8-diazadispiro[2.2.4^{6}.2^{3}]dodec-7-ene (321): To a solution of 2,2-dimethyl-1-oxaspiro[2.5]octan-6-one (0.734 g, 4.76 mmol, 1 equiv.) in MeOH (20 mL) was added acetic hydrazide (0.388 g, 5.24 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 2 h, then cooled to 0 °C. (Diacetoxy)iodobenzene (1.69 g, 5.24 mmol, 1.1 equiv.) was added portionwise, then the mixture stirred further at this temperature for 1 h. The mixture was evaporated under reduced pressure and the residue purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) to provide the title compound as an inseparable mixture of diastereomers (1:1) as a white amorphous solid (1.03 g, 4.29 mmol, 90%).

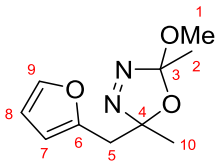
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.15 and 3.14 (two s, 3 H, H1), 2.48 (td, *J* = 12.7, 4.4 Hz, 0.5 H, H5a of diastereomer A), 2.35 (td, *J* = 12.7, 4.4 Hz, 0.5 H, H12a of diastereomer A), 2.18 – 2.11 (m, 0.5 H, H6a of diastereomer B), 2.11 – 1.94 (m, 2.5 H, H6/H11 of diastereomer A, H11a of diastereomer B, H12 of diastereomer B), 1.94 – 1.79 (m, 3 H, H6/H11 of diastereomer A, H5 of diastereomer B, H6b of diastereomer B, H11b of diastereomer B), 1.75 – 1.68 (m, 0.5 H, H5b of diastereomer A), 1.67 and 1.66 (two s, 3 H, H2), 1.48 – 1.42 (m, 0.5 H, H12b of diastereomer A), 1.42 and 1.38 (two s, 3 H, H9/H10), 1.41 and 1.37 (two s, 3 H, H9/H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.1 and 133.0 (C3), 121.1 and 120.8 (C4), 64.8 and 64.3 (C7), 63.0 and 62.9 (C8), 50.73 and 50.70 (C1), 33.7 and 32.2 (C5/C12), 32.4 and 31.1 (C5/C12), 27.7 and 26.8 (C6/C11), 27.6 and 26.7 (C6/C11), 24.0 and 23.9 (C2), 20.9 and 20.7 (C9 and C10).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 1574 (w), 1439 (m), 1378 (m), 1359 (w), 1225 (m), 1201 (s), 1157 (m), 1102 (s), 1056 (s), 1003 (w), 979 (w), 954 (w), 907 (s), 889 (m), 871 (m), 770 (w).

HRMS (ESI): calculated for $C_{12}H_{20}N_2O_3Na$ $[M+Na]^+$ 263.1366, found 263.1361.

R_f = 0.40 (20% EtOAc/hexane).



322

2-(Furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (322): Following the general procedure for oxadiazoline synthesis using 2-furylacetone (2.48 g, 20.0 mmol), purified by silica gel column chromatography (eluent: hexane → 10% EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (2:1) as an orange oil (3.36 g, 16.0 mmol, 80%).

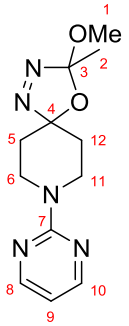
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 1.3 Hz, 0.33 H, H9 of diastereomer A), 7.32 (d, *J* = 1.3 Hz, 0.67 H, H9 of diastereomer B), 6.35 – 6.31 (m, 0.33 H, H8 of diastereomer A), 6.31 – 6.26 (m, 0.67 H, H8 of diastereomer B), 6.22 (d, *J* = 3.1 Hz, 0.33 H, H7 of diastereomer A), 6.11 (d, *J* = 3.2 Hz, 0.67 H, H7 of diastereomer B), 3.33 (d, *J* = 15.2 Hz, 0.33 H, H5a of diastereomer A), 3.21 – 3.14 (m, 1.33 H, H5 of diastereomer B), 3.13 and 3.12 (two s, 3 H, H1), 3.05 (d, *J* = 15.2 Hz, 0.33 H, H5b of diastereomer A), 1.63 and 1.34 (two s, 3 H, H2), 1.60 and 1.44 (two s, 3 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 149.2 and 149.0 (C6), 142.2 and 142.1 (C9), 134.5 and 134.1 (C3), 121.3 and 120.5 (C4), 110.73 and 110.71 (C8), 109.3 and 109.1 (C7), 50.8 and 50.7 (C1), 37.1 and 36.4 (C5), 23.4 and 22.3 (C2), 22.8 (C10).

FTIR (ν_{max}, cm^{-1}): 2990 (w), 2945 (w), 1597 (w), 1573 (w), 1505 (w), 1455 (w), 1377 (m), 1188 (m), 1146 (s), 1089 (m), 1054 (s), 1012 (m), 968 (m), 939 (m), 907 (s), 886 (w), 865 (m), 835 (w), 812 (w).

HRMS (ESI): calculated for $C_{10}H_{15}N_2O_3$ $[M+H]^+$ 211.1077, found 211.1076.

R_f = 0.33 (10% EtOAc/hexane).



323

3-Methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (323): Following the general procedure for oxadiazoline synthesis using 1-(pyrimidin-2-yl)piperidin-4-one (0.98 g, 5.5 mmol), purified by silica gel column chromatography (eluent: hexane → 30% EtOAc/hexane) provided the title compound as a white crystalline solid (1.25 g, 4.7 mmol, 86%), m.p. 96-98 °C.

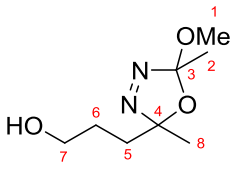
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32 (d, *J* = 4.8 Hz, 2 H, H8 and H10), 6.51 (t, *J* = 4.8 Hz, 1 H, H9), 4.44 – 4.33 (m, 2 H, H6/H11), 3.87 – 3.80 (m, 2 H, H6/H11), 3.15 (s, 3 H, H1), 2.23 – 2.16 (m, 1 H, H5/H12), 2.07 – 2.00 (m, 1 H, H5/H12), 1.79 – 1.72 (m, 1 H, H5/H12), 1.68 (s, 3 H, H2), 1.59 – 1.53 (m, 1 H, H5/H12).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.5 (C7), 158.0 (C8 and C10), 133.3 (C3), 120.3 (C4), 110.2 (C9), 50.8 (C1), 41.12 (C6/C11), 41.07 (C6/C11), 34.2 (C5/C12), 33.1 (C5/C12), 23.9 (C2).

FTIR (ν_{max}, cm^{-1}): 2999 (w), 2962 (w), 2865 (w), 1585 (s), 1548 (s), 1499 (s), 1456 (m), 1394 (w), 1365 (s), 1307 (w), 1262 (m), 1232 (m), 1201 (m), 1157 (m), 1132 (m), 1118 (m), 1096 (m), 1054 (m), 984 (w), 950 (w), 930 (m), 907 (m), 865 (w), 798 (m), 782 (w).

HRMS (ESI): calculated for $C_{12}H_{18}N_5O_2$ $[M+H]^+$ 264.1455, found 264.1465.

R_f = 0.44 (30% EtOAc/hexane).



324

3-(5-Methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)propan-1-ol (324): Following the general procedure for oxadiazoline synthesis using 5-hydroxy-2-pentanone (4.09 g, 40.0 mmol), purified by silica gel column chromatography (eluent: hexane → 40%

EtOAc/hexane) provided the title compound as an inseparable mixture of diastereomers (1.4:1) as a colourless oil (4.07 g, 21.6 mmol, 54%).

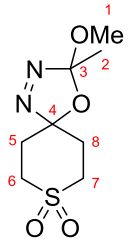
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.73 – 3.63 (m, 2 H, H7), 3.18 and 3.17 (two s, 3 H, H1), 2.12 – 1.51 (m, 5 H, H5, H6 and OH), 1.68 and 1.64 (two s, 3 H, H2), 1.57 and 1.46 (two s, 3 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.4 and 133.3 (C3), 122.4 and 122.3 (C4), 62.59 and 62.56 (C7), 50.9 and 50.8 (C1), 34.9 and 34.1 (C5), 27.2 and 27.0 (C6), 23.4 and 22.8 (C2), 22.5 and 22.3 (C8).

FTIR (ν_{max}, cm^{-1}): 3431 (br w, OH), 2990 (w), 2945 (w), 1574 (w), 1455 (w), 1377 (m), 1197 (s), 1150 (s), 1102 (w), 1053 (s), 1024 (s), 963 (w), 907 (s), 868 (m).

HRMS (ESI): calculated for $C_8H_{16}N_2O_3Na$ $[M+Na]^+$ 211.1053, found 211.1055.

R_f = 0.26 (40% EtOAc/hexane).



325

3-Methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene 8,8-dioxide (325): To a solution of 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (1.01 g, 5.0 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) was added *m*-CPBA (3.97 g, 11.5 mmol, 2.3 equiv., 50% purity) in four portions at r.t. and the mixture stirred further for 3 h. The mixture was filtered to remove precipitated *m*-chlorobenzoic acid, washed on the filter with CH_2Cl_2 (2 × 15 mL), then the filtrate washed with saturated aqueous Na_2CO_3 solution (50 mL). The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) to provide the title compound as a white amorphous solid (1.13 g, 4.83 mmol, 97%), m.p. 122-123 °C.

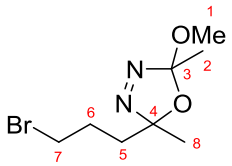
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.36 – 3.23 (m, 4 H, H6 and H7), 3.20 (s, 3 H, H1), 2.80 (ddd, *J* = 14.6, 10.8, 3.9 Hz, 1 H, H5/H8), 2.74 – 2.64 (m, 1 H, H5/H8), 2.17 – 2.10 (m, 1 H, H5/H8), 1.98 – 1.90 (m, 1 H, H5/H8), 1.70 (s, 3 H, H2).

^{13}C NMR (150 MHz, $CDCl_3$): δ 134.9 (C3), 117.3 (C4), 51.2 (C1), 48.2 (C6/C7), 48.1 (C6/C7), 32.8 (C5/C8), 32.0 (C5/C8), 23.1 (C2).

FTIR (ν_{max}, cm^{-1}): 2989 (w), 2944 (w), 1576 (w), 1436 (w), 1402 (w), 1382 (w), 1358 (w), 1337 (m), 1298 (s), 1225 (m), 1203 (m), 1133 (s), 1087 (s), 1051 (m), 1012 (w), 950 (m), 930 (w), 903 (m), 852 (s), 768 (w).

HRMS (ESI): calculated for $C_8H_{15}N_2O_4S$ $[M+H]^+$ 235.0747, found 235.0750.

***R*$_f$** = 0.33 (40% EtOAc/hexane).



326

2-(3-Bromopropyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (326): To a solution of 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)propan-1-ol (**324**) (0.941 g, 5.0 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at r.t. was added carbon tetrabromide (1.99 g, 6.0 mmol, 1.2 equiv.) then triphenylphosphine (1.57 g, 6.0 mmol, 1.2 equiv.) in three portions. The mixture was further stirred for 1 h, evaporated under reduced pressure and the residue purified by silica gel column chromatography (eluent: 5% EtOAc/hexane) to provide the title compound as inseparable diastereomers (1.4:1) as a colourless oil (0.991 g, 3.95 mmol, 79%).

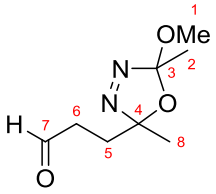
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.49 – 3.39 (m, 2 H, H7), 3.20 and 3.18 (two s, 3 H), 2.20 – 1.76 (m, 4 H, H5 and H6), 1.68 and 1.64 (two s, 3 H, H2), 1.56 and 1.44 (two s, 3 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 133.7 and 133.5 (C3), 121.9 and 121.7 (C4), 51.0 and 50.8 (C1), 36.8 and 36.2 (C5), 33.4 and 33.2 (C7), 27.3 and 27.2 (C6), 23.3 and 22.68 (C2), 22.70 and 22.4 (C8).

FTIR (ν_{max}, cm^{-1}): 2990 (w), 2943 (w), 2837 (w), 1574 (w), 1455 (w), 1377 (m), 1298 (w), 1264 (w), 1239 (m), 1196 (s), 1152 (s), 1089 (m), 1053 (s), 1003 (w), 975 (w), 909 (s), 869 (m), 835 (w), 767 (w).

HRMS (ESI): calculated for $C_8H_{16}N_2O_2Br$ $[M+H]^+$ 251.0390, found 251.0378.

***R*$_f$** = 0.22 (5% EtOAc/hexane).



327

3-(5-Methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)propanal (327): To a solution of oxalyl chloride (1.28 mL, 15.0 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (15 mL) at -78 °C was added slowly dropwise a solution of DMSO (1.56 mL, 22.0 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (15 mL), keeping the internal temperature below -60 °C. The mixture was stirred further for 5 min. A solution of 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)propan-1-ol (**324**) (1.88 g, 10.0 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (15 mL) was added slowly dropwise and stirred further for 15 min. Triethylamine (6.9 mL, 50.0 mmol, 5 equiv.) was then added, stirred at -78 °C for 30 min, warmed to r.t. and quenched with water (40 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) to provide the title compound as inseparable diastereomers (1.4:1) as a pale yellow oil (1.36 g, 7.3 mmol, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.81 – 9.75 (m, 1 H, H7), 3.21 and 3.20 (two s, 3 H, H1), 2.73 (dddd, *J* = 18.3, 9.7, 5.7, 0.6 Hz, 0.4 H, H6a of diastereomer A), 2.62 (dddd, *J* = 18.3, 9.7, 5.7, 0.8 Hz, 0.4 H, H6b of diastereomer A), 2.58 – 2.46 (m, 1.2 H, H6 of diastereomer B), 2.33 – 2.25 (m, 0.4 H, H5a of diastereomer A), 2.25 – 2.18 (m, 0.6 H, H5a of diastereomer B), 2.11 – 2.01 (m, 1 H, H5b of diastereomer A and B), 1.68 and 1.64 (two s, 3 H, H2), 1.55 and 1.44 (two s, 3 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 200.6 and 200.5 (C7), 133.8 and 133.5 (C3), 121.46 and 121.45 (C4), 51.1 and 50.9 (C1), 38.5 and 38.3 (C6), 30.3 and 29.6 (C5), 23.0 and 22.3 (C2), 22.9 and 22.5 (C8).

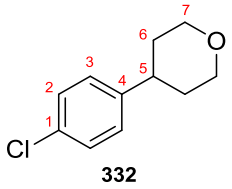
FTIR (ν_{max}, cm^{-1}): 2989 (w), 2943 (w), 2837 (w), 1723 (s, C=O), 1574 (w), 1455 (w), 1415 (w), 1378 (m), 1191 (s), 1147 (s), 1101 (m), 1053 (s), 1023 (m), 961 (w), 908 (s), 867 (m).

HRMS (ESI): calculated for $C_8H_{15}N_2O_3$ $[M+H]^+$ 187.1077, found 187.1072.

R_f = 0.43 (30% EtOAc/hexane).

5.4.2. Synthetic procedures and characterisation for protodeboronative cross-couplings

General procedure for protodeboronative coupling: A solution of the appropriate oxadiazoline (1.0 mmol, 2 equiv.), boronic acid (0.5 mmol, 1.0 equiv.) and DIPEA (0.17 mL, 1.0 mmol, 2 equiv.) in CH_2Cl_2 (10 mL) was pumped at a flow rate of 0.125 mL min^{-1} through a Vapourtec UV-150 photochemical reactor (10 mL reactor volume, FEP tubing) held at 10 °C and the reactor output was monitored using a FlowIR® device (SiComp head, 2100-2000 cm^{-1} and 1750-1700 cm^{-1}). After 80 min once the reaction mixture has fully been taken up by the pump, the input was swapped to CH_2Cl_2 solvent. When the FlowIR® showed that the reaction plug was exiting the output stream (by monitoring the MeOAc C=O stretch at 1750-1700 cm^{-1}), the reaction plug was directed into a sealed vial containing TBAF (1.5 mL, 1.5 mmol, 3.0 equiv., 1.0 M in THF) and stirred for 16 h. The mixture was then evaporated under reduced pressure, the residue redissolved in EtOAc (5 mL) and filtered through a pad of Celite, eluting with EtOAc. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography.



332

4-(4-Chlorophenyl)tetrahydro-2*H*-pyran (332): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (69.9 mg, 0.355 mmol, 71%). Data are consistent with a reported example.[224]

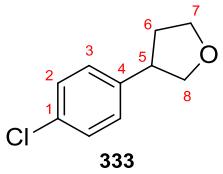
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.4 Hz, 2 H, H2), 7.15 (d, *J* = 8.4 Hz, 2 H, H3), 4.17 – 4.00 (m, 2 H, H7a), 3.52 (td, *J* = 11.5, 2.7 Hz, 2 H, H7b), 2.73 (tt, *J* = 11.4, 4.5 Hz, 1 H, H5), 1.85 – 1.68 (m, 4 H, H6a and H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.4 (C4), 132.0 (C1), 128.7 (C2), 128.2 (C3), 68.7 (C7), 41.1 (C5), 34.0 (C6).

FTIR (ν_{max}, cm^{-1}): 2938 (m), 2842 (m), 2757 (w), 1493 (m), 1466 (w), 1442 (w), 1430 (w), 1386 (m), 1365 (w), 1303 (w), 1263 (w), 1237 (m), 1197 (w), 1129 (m), 1089 (s), 1013 (s), 980 (m), 911 (w), 896 (m), 838 (m), 824 (m), 792 (m).

HRMS (ESI): calculated for $C_{11}H_{14}OCl$ $[M+H]^+$ 197.0728, found 197.0737.

R_f = 0.39 (10% EtOAc/hexane).



333

3-(4-Chlorophenyl)tetrahydrofuran (333): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,7-dioxa-1,2-diazaspiro[4.4]non-1-ene (**304**) (0.172 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (53.2 mg, 0.291 mmol, 58%).

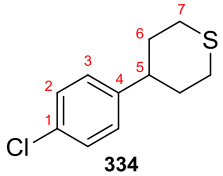
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2 H, H2), 7.18 (d, *J* = 8.5 Hz, 2 H, H3), 4.11 (dd, *J* = 8.5, 7.6 Hz, 1 H, H8a), 4.05 (td, *J* = 8.4, 4.6 Hz, 1 H, H7a), 3.94 – 3.87 (m, 1 H, H7b), 3.69 (dd, *J* = 8.5, 7.2 Hz, 1 H, H8b), 3.42 – 3.32 (m, 1 H, H5), 2.41 – 2.31 (m, 1 H, H6a), 1.99 – 1.92 (m, 1 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.5 (C4), 132.3 (C1), 128.8 (C2), 128.7 (C3), 74.7 (C8), 68.5 (C7), 44.5 (C5), 34.8 (C6).

FTIR (ν_{max}, cm^{-1}): 2971 (w), 2938 (w), 2861 (w), 1493 (s), 1452 (w), 1413 (w), 1362 (w), 1181 (w), 1091 (s), 1055 (s), 1014 (s), 970 (w), 903 (m), 822 (s).

HRMS (ESI): calculated for $C_{10}H_{12}OCl$ $[M+H]^+$ 183.0571, found 183.0573.

R_f = 0.29 (10% EtOAc/hexane).

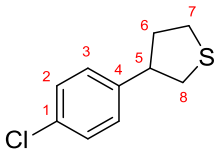


334

4-(4-Chlorophenyl)tetrahydro-2*H*-thiopyran (334): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (**305**) (0.202 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol),

purified by silica gel column chromatography (eluent: 2% EtOAc/hexane) provided the title compound as a white crystalline solid (53.2 mg, 0.291 mmol, 58%), m.p. 69-70 °C (lit. m.p.[225] 70-71 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2 H, H2), 7.12 (d, *J* = 8.4 Hz, 2 H, H3), 2.87 – 2.79 (m, 2 H, H7a), 2.72 – 2.66 (m, 2 H, H7b), 2.50 (tt, *J* = 12.5, 3.1 Hz, 1 H, H5), 2.15 – 2.07 (m, 2 H, H6a), 1.82 (qd, *J* = 12.5, 3.2 Hz, 2 H, H6b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 145.4 (C4), 132.0 (C1), 128.7 (C2), 128.3 (C3), 43.9 (C5), 35.2 (C6), 29.3 (C7).
FTIR (ν_{max}, cm^{-1}): 2926 (w), 2904 (w), 2841 (w), 1596 (w), 1493 (s), 1441 (w), 1428 (w), 1409 (w), 1306 (w), 1269 (m), 1174 (w), 1093 (s), 1013 (m), 985 (w), 952 (m), 902 (w), 825 (s), 783 (m).
HRMS (ESI): calculated for $C_{11}H_{14}SCl$ $[M+H]^+$ 213.0499, found 213.0497.
R_f = 0.19 (2% EtOAc/hexane).



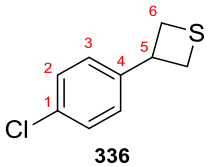
335

3-(4-Chlorophenyl)tetrahydrothiophene (335): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (**306**) (0.188 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 2% EtOAc/hexane) provided the title compound as a white crystalline solid (59.4 mg, 0.299 mmol, 60%), m.p. 42-44 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2 H, H2), 7.22 (d, *J* = 8.5 Hz, 2 H, H3), 3.35 – 3.26 (m, 1 H, H5), 3.15 (dd, *J* = 10.5, 6.8 Hz, 1 H, H8a), 3.00 – 2.94 (m, 2 H, H7a and H7b), 2.86 (dd, *J* = 10.5, 9.6 Hz, 1 H, H8b), 2.42 – 2.35 (m, 1 H, H6a), 2.06 – 1.97 (m, 1 H, H6b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 140.7 (C4), 132.5 (C1), 128.8 (C2), 128.5 (C3), 49.1 (C5), 38.1 (C6), 37.7 (C8), 30.9 (C7).
FTIR (ν_{max}, cm^{-1}): 2932 (w), 2860 (w), 1493 (s), 1456 (w), 1437 (w), 1410 (w), 1262 (w), 1211 (w), 1091 (m), 1014 (m), 886 (w), 865 (w), 824 (m).

HRMS (ESI): calculated for $C_{10}H_{12}SCl$ $[M+H]^+$ 199.0343, found 199.0345.

$\boldsymbol{R_f}$ = 0.38 (2% EtOAc/hexane).



336

3-(4-Chlorophenyl)thietane (336): Following the general procedure for protodeboronative coupling using 7-methoxy-7-methyl-8-oxa-2-thia-5,6-diazaspiro[3.4]oct-5-ene (**307**) (0.174 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 2% EtOAc/hexane) provided the title compound as a colourless oil (38.9 mg, 0.211 mmol, 42%).

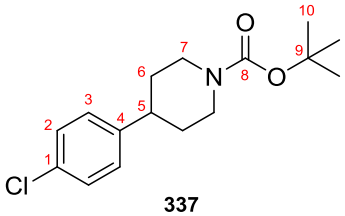
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.5 Hz, 2 H, H2), 7.23 (d, *J* = 8.5 Hz, 2 H, H3), 4.52 (qn, *J* = 9.0 Hz, 1 H, H5), 3.53 (t, *J* = 9.0 Hz, 2 H, H6a), 3.36 (t, *J* = 9.0 Hz, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 142.6 (C4), 132.8 (C1), 128.9 (C2), 127.4 (C3), 44.6 (C5), 33.1 (C6).

FTIR (ν_{max}, cm^{-1}): 2977 (w), 2938 (w), 2860 (w), 1595 (w), 1492 (s), 1451 (w), 1409 (w), 1326 (w), 1236 (w), 1174 (m), 1091 (s), 1014 (s), 941 (w), 908 (w), 846 (m), 816 (s).

HRMS (ESI): calculated for $C_9H_{10}SCl$ $[M+H]^+$ 185.0186, found 185.0179.

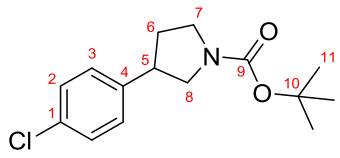
$\boldsymbol{R_f}$ = 0.33 (2% EtOAc/hexane).



337

***tert*-Butyl 4-(4-chlorophenyl)piperidine-1-carboxylate (337):** Following the general procedure for protodeboronative coupling using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (**308**) (0.285 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless gum (124.4 mg, 0.421 mmol, 84%). Data are consistent with a reported example.[24]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.12 (d, *J* = 8.5 Hz, 2 H, H3), 4.23 (br s, 2 H, H7a), 2.78 (br s, 2 H, H7b), 2.61 (tt, *J* = 12.2, 3.5 Hz, 1 H, H5), 1.78 (br d, *J* = 12.8 Hz, 2 H, H6a), 1.62 – 1.52 (br m, 2 H, H6b), 1.47 (s, 9 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 154.9 (C8), 144.3 (C4), 132.0 (C1), 128.7 (C2), 128.2 (C3), 79.6 (C9), 45.5 – 43.4 (br, C7), 42.2 (C5), 33.2 (br, C6), 28.6 (C10).
FTIR (ν_{max}, cm^{-1}): 2976 (w), 2934 (w), 2853 (w), 1687 (s, C=O), 1493 (m), 1466 (m), 1445 (m), 1420 (m), 1365 (m), 1320 (w), 1294 (w), 1276 (m), 1230 (s), 1161 (s), 1123 (m), 1091 (m), 1012 (m), 987 (w), 933 (w), 908 (w), 884 (w), 862 (w), 824 (m), 769 (w).
HRMS (ESI): calculated for $C_{16}H_{22}NO_2ClNa$ $[M+Na]^+$ 318.1231, found 318.1229.
R_f = 0.30 (10% EtOAc/hexane).



338

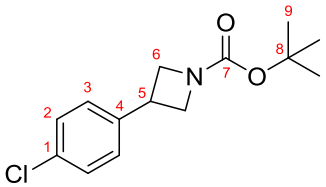
***tert*-Butyl 3-(4-chlorophenyl)pyrrolidine-1-carboxylate (338):** Following the general procedure for protodeboronative coupling using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,7-triazaspiro[4.4]non-1-ene-7-carboxylate (**309**) (0.271 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless gum (84.6 mg, 0.300 mmol, 60%). Data are consistent with a reported example.[226]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.3 Hz, 2 H, H2), 7.15 (two superimposed d from rotamers, *J* = 8.3 Hz, 2 H, H3), 3.88 – 3.79 (m, 0.5 H, H8a of rotamer A), 3.79 – 3.72 (m, 0.5 H, H8a of rotamer B), 3.66 – 3.58 (m, 0.5 H, H7a of rotamer B), 3.57 – 3.49 (m, 0.5 H, H7a of rotamer A), 3.44 – 3.34 (m, 1 H, H7b of rotamers A and B), 3.34 – 3.25 (m, 1.5 H, H5 of rotamers A and B, H8b of rotamer A), 3.22 (t, *J* = 9.9 Hz, 0.5 H, H8b of rotamer B), 2.30 – 2.18 (m, 1 H, H6a of rotamers A and B), 1.99 – 1.87 (m, 1 H, H6b of rotamers A and B), 1.47 and 1.46 (two superimposed s from rotamers, 9 H, H11).
^{13}C NMR (150 MHz, $CDCl_3$): δ 154.6 (C9), 140.1 (C4), 132.6 (C1), 128.8 (C2), 128.5 (C3), 79.4 (C10), 52.6 and 51.8 (rotameric, C8), 45.9 and 45.6 (rotameric, C7), 43.8 and 42.9 (rotameric, C5), 33.4 and 32.5 (rotameric, C6), 28.6 (C11).

FTIR (ν_{max}, cm^{-1}): 2976 (w), 2880 (w), 1688 (s, C=O), 1494 (m), 1478 (w), 1454 (w), 1399 (s), 1365 (s), 1342 (w), 1254 (w), 1164 (s), 1122 (s), 1092 (s), 1014 (m), 984 (w), 922 (w), 879 (m), 826 (m), 772 (m).

HRMS (ESI): calculated for $C_{15}H_{20}NO_2ClNa$ $[M+Na]^+$ 304.1075, found 304.1063.

R_f = 0.22 (10% EtOAc/hexane).



339

***tert*-Butyl 3-(4-chlorophenyl)azetidine-1-carboxylate (339):** Following the general procedure for protodeboronative coupling using *tert*-butyl 7-methoxy-7-methyl-8-oxa-2,5,6-triazaspiro[3.4]oct-5-ene-2-carboxylate (**310**) (0.257 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a colourless gum (70.9 mg, 0.265 mmol, 53%).

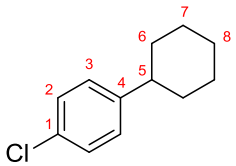
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.5 Hz, 2 H, H2), 7.23 (d, *J* = 8.5 Hz, 2 H, H3), 4.31 (t, *J* = 8.7 Hz, 2 H, H6a), 3.97 – 3.87 (dd, *J* = 8.7, 6.0 Hz, 2 H, H6b), 3.68 (tt, *J* = 8.7, 6.0 Hz, 1 H, H5), 1.45 (s, 9 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.4 (C7), 140.8 (C4), 132.7 (C1), 128.9 (C2), 128.3 (C3), 79.8 (C8), 57.2 and 56.0 (br, C6), 33.0 (C5), 28.5 (C9).

FTIR (ν_{max}, cm^{-1}): 2976 (w), 2887 (w), 1697 (s, C=O), 1494 (m), 1478 (w), 1457 (w), 1390 (s), 1365 (s), 1338 (m), 1297 (w), 1250 (w), 1129 (s), 1093 (s), 1060 (w), 1014 (m), 967 (w), 909 (w), 859 (w), 821 (m), 773 (m).

HRMS (ESI): calculated for $C_{14}H_{18}NO_2ClNa$ $[M+Na]^+$ 290.0918, found 290.0910.

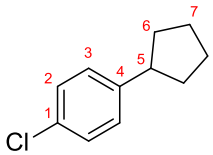
R_f = 0.43 (20% EtOAc/hexane).



340

1-Chloro-4-cyclohexylbenzene (340): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.5]dec-1-ene (**311**) (0.184 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (71.9 mg, 0.369 mmol, 74%). Data are consistent with a reported example.[227]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2 H, H2), 7.15 (d, *J* = 8.4 Hz, 2 H, H3), 2.54 – 2.44 (m, 1 H, H5), 1.91 – 1.81 (m, 4 H, H6a and H7a), 1.80 – 1.73 (m, 1 H, H8a), 1.46 – 1.34 (m, 4 H, H6b and H7b), 1.32 – 1.20 (m, 1 H, H8b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 146.6 (C4), 131.4 (C1), 128.5 (C2), 128.3 (C3), 44.1 (C5), 34.6 (C6), 26.9 (C7), 26.2 (C8).
FTIR (ν_{max}, cm^{-1}): 2923 (m), 2851 (m), 1492 (m), 1448 (m), 1409 (w), 1351 (w), 1262 (w), 1178 (w), 1090 (m), 1014 (m), 1000 (w), 892 (w), 818 (s), 775 (w).
HRMS (ESI): calculated for $C_{12}H_{16}Cl$ $[M+H]^+$ 195.0935, found 195.0941.
R_f = 0.76 (hexane).



341

1-Chloro-4-cyclopentylbenzene (341): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.4]non-1-ene (**312**) (0.170 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (52.0 mg, 0.288 mmol, 58%). Data are consistent with a reported example.[155]

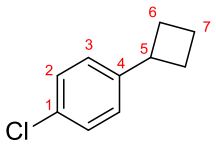
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2 H, H2), 7.17 (d, *J* = 8.4 Hz, 2 H, H3), 3.01 – 2.90 (m, 1 H, H5), 2.10 – 2.01 (m, 2 H, H6a), 1.86 – 1.75 (m, 2 H, H7a), 1.74 – 1.62 (m, 2 H, H7b), 1.60 – 1.49 (m, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.1 (C4), 131.3 (C1), 128.6 (C3), 128.4 (C2), 45.5 (C5), 34.7 (C6), 25.6 (C7).

FTIR (ν_{max}, cm^{-1}): 2953 (m), 2870 (m), 1597 (w), 1493 (s), 1451 (w), 1337 (w), 1179 (w), 1091 (s), 1014 (m), 947 (w), 818 (s).

HRMS (ESI): calculated for $C_{11}H_{14}Cl$ $[M+H]^+$ 181.0779, found 181.0784.

***R*$_f$** = 0.75 (hexane).



342

1-Chloro-4-cyclobutylbenzene (342): Following the general procedure for protodeboronative coupling using 7-methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (**313**) (0.156 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (46.0 mg, 0.276 mmol, 55%).

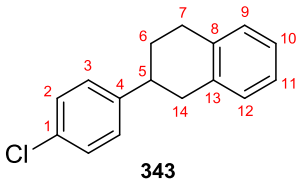
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2 H, H2), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 3.51 (qn, *J* = 8.7 Hz, 1 H, H5), 2.40 – 2.30 (m, 2 H, H6a), 2.16 – 2.07 (m, 2 H, H6b), 2.07 – 1.97 (m, 1 H, H7a), 1.90 – 1.82 (m, 1 H, H7b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.8 (C4), 131.4 (C1), 128.4 (C2), 127.8 (C3), 39.9 (C5), 29.9 (C6), 18.3 (C7).

FTIR (ν_{max}, cm^{-1}): 2964 (m), 2940 (m), 2863 (w), 1596 (w), 1491 (m), 1445 (w), 1399 (w), 1333 (w), 1243 (w), 1091 (s), 1014 (m), 916 (w), 872 (w), 820 (s), 752 (w).

HRMS (ESI): calculated for $C_{10}H_{12}Cl$ $[M+H]^+$ 167.0622, found 167.0617.

***R*$_f$** = 0.78 (hexane).



343

2-(4-Chlorophenyl)-1,2,3,4-tetrahydronaphthalene (343): Following the general procedure for protodeboronative coupling using 5'-methoxy-5'-methyl-3,4-dihydro-1*H*,5'*H*-spiro[naphthalene-2,2'-[1,3,4]oxadiazole] (**314**) (0.232 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a pale brown amorphous solid (116.2 mg, 0.479 mmol, 96%), m.p. 93-94 °C.

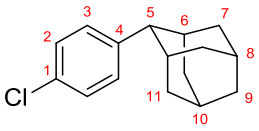
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2 H, H2), 7.21 (d, *J* = 8.4 Hz, 2 H, H3), 7.17 – 7.07 (m, 4 H, H9, H10, H11 and H12), 3.06 – 2.84 (m, 5 H, H5, H7 and H14), 2.15 – 2.09 (m, 1 H, H6a), 1.96 – 1.87 (m, 1 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.2 (C4), 136.4 (C8/C13), 136.2 (C8/C13), 132.0 (C1), 129.14 (C9/C10/C11/C12), 129.09 (C9/C10/C11/C12), 128.7 (C2), 128.4 (C3), 126.0 (C9/C10/C11/C12), 125.9 (C9/C10/C11/C12), 40.3 (C5), 37.7 (C14), 30.5 (C6), 29.7 (C7).

FTIR (ν_{max}, cm^{-1}): 3019 (w), 2924 (w), 2836 (w), 1599 (w), 1579 (w), 1492 (s), 1451 (m), 1436 (m), 1410 (w), 1344 (w), 1297 (w), 1216 (s), 1180 (w), 1108 (w), 1088 (m), 1056 (w), 1036 (w), 1014 (m), 951 (w), 924 (w), 890 (w), 837 (w), 818 (s), 797 (w).

HRMS (ESI): calculated for $C_{16}H_{16}Cl$ $[M+H]^+$ 243.0935, found 243.0934.

R_f = 0.47 (hexane).



344

2-(4-Chlorophenyl)adamantane (344): Following the general procedure for protodeboronative coupling using 5'-methoxy-5'-methyl-5'*H*-spiro[adamantane-2,2'-[1,3,4]oxadiazole] (**315**) (0.236 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (91.0 mg, 0.369 mmol, 74%).

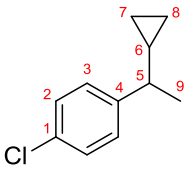
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (appears s, 4 H, H2 and H3), 2.97 (br s, 1 H, H5), 2.44 (br s, 2 H, H6), 2.05 – 1.97 (m, 3 H, H10 and H11a), 1.94 (br d, *J* = 11.1 Hz, 2 H, H11b), 1.83 – 1.76 (m, 5 H, H7a, H8 and H9), 1.57 (br d, *J* = 12.2 Hz, 2 H, H7b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.0 (C4), 130.9 (C1), 128.4 (C2/C3), 128.3 (C2/C3), 46.5 (C5), 39.2 (C11), 37.9 (C9), 32.0 (C7), 31.2 (C6), 28.1 (C10), 27.8 (C8).

FTIR (ν_{max}, cm^{-1}): 2902 (s), 2849 (m), 1594 (w), 1568 (w), 1493 (s), 1469 (w), 1450 (m), 1400 (w), 1355 (w), 1342 (w), 1329 (w), 1282 (w), 1227 (w), 1208 (w), 1092 (m), 1070 (w), 1040 (w), 1013 (m), 971 (m), 950 (w), 913 (w), 870 (w), 851 (m), 832 (m), 818 (m), 784 (m), 761 (m).

HRMS (ESI): calculated for $C_{16}H_{20}Cl$ $[M+H]^+$ 247.1248, found 247.1256.

***R*$_f$** = 0.70 (hexane).



345

1-Chloro-4-(1-cyclopropylethyl)benzene (345): Following the general procedure for protodeboronative coupling using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**316**) (0.236 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (78.0 mg, 0.432 mmol, 86%).

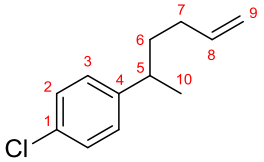
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.4 Hz, 2 H, H2), 7.20 (d, *J* = 8.4 Hz, 2 H, H3), 2.04 – 1.93 (m, 1 H, H5), 1.33 (d, *J* = 7.1 Hz, 3 H, H9), 0.96 – 0.87 (m, 1 H, H6), 0.61 – 0.54 (m, 1 H, H7/H8), 0.48 – 0.40 (m, 1 H, H7/H8), 0.25 – 0.18 (m, 1 H, H7/H8), 0.17 – 0.11 (m, 1 H, H7/H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.9 (C4), 131.6 (C1), 128.5 (C2/C3), 128.4 (C2/C3), 44.2 (C5), 21.6 (C9), 18.6 (C6), 4.8 (C7/C8), 4.4 (C7/C8).

FTIR (ν_{max}, cm^{-1}): 3077 (w), 3000 (w), 2964 (w), 2875 (w), 1492 (s), 1454 (w), 1428 (w), 1410 (w), 1370 (w), 1282 (w), 1168 (w), 1091 (s), 1036 (w), 1014 (s), 973 (w), 926 (m), 822 (s), 791 (w), 753 (w).

HRMS (ESI): calculated for $C_{11}H_{14}Cl$ $[M+H]^+$ 181.0779, found 181.0783.

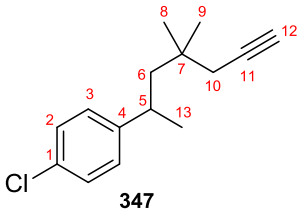
***R*$_f$** = 0.69 (hexane).



346

1-Chloro-4-(hex-5-en-2-yl)benzene (346): Following the general procedure for protodeboronative coupling using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**317**) (0.184 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (86.6 mg, 0.445 mmol, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2 H, H2), 7.12 (d, *J* = 8.4 Hz, 2 H, H3), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H, H8), 5.00 – 4.93 (m, 2 H, H9), 2.74 – 2.66 (m, 1 H, H5), 2.02 – 1.89 (m, 2 H, H7), 1.71 – 1.60 (m, 2 H, H6), 1.23 (d, *J* = 7.0 Hz, 3 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 145.9 (C4), 138.6 (C8), 131.6 (C1), 128.6 (C2/C3), 128.5 (C2/C3), 114.7 (C9), 38.9 (C5), 37.5 (C6), 31.9 (C7), 22.3 (C10).
FTIR (ν_{max}, cm^{-1}): 2960 (w), 2925 (w), 1641 (w), 1493 (m), 1456 (w), 1411 (w), 1376 (w), 1344 (w), 1300 (w), 1180 (w), 1094 (m), 1014 (m), 993 (w), 910 (m), 826 (s), 788 (w), 760 (w).
HRMS (ESI): calculated for $C_{12}H_{16}Cl$ $[M+H]^+$ 195.0935, found 195.0935.
***R*$_f$** = 0.72 (hexane).



347

1-Chloro-4-(4,4-dimethylhept-6-yn-2-yl)benzene (347): Following the general procedure for protodeboronative coupling using 2-(2,2-dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**318**) (0.224 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (100.2 mg, 0.427 mmol, 85%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2 H, H2), 7.15 (d, *J* = 8.5 Hz, 2 H, H3), 2.86 – 2.78 (m, 1 H, H5), 2.02 (dd, *J* = 16.4, 2.8 Hz, 1 H, H10a), 1.97 (t, *J* = 2.8 Hz, 1 H,

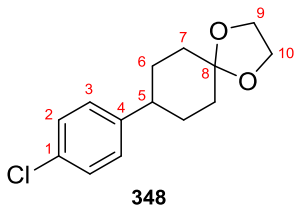
H12), 1.93 (dd, *J* = 16.4, 2.8 Hz, 1 H, H10b), 1.79 (dd, *J* = 14.3, 8.6 Hz, 1 H, H6a), 1.63 (dd, *J* = 14.3, 4.2 Hz, 1 H, H6b), 1.22 (d, *J* = 7.0 Hz, 3 H, H13), 0.89 (s, 3 H, H8/H9), 0.85 (s, 3 H, H8/H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.5 (C4), 131.4 (C1), 128.6 (C2/C3), 128.5 (C2/C3), 82.6 (C11), 70.2 (C12), 48.9 (C6), 36.2 (C5), 34.2 (C7), 32.4 (C10), 27.5 (two superimposed s, C8 and C9), 26.0 (C13).

FTIR (ν_{max}, cm^{-1}): 3307 (w, alkyne CH), 2959 (m), 2926 (w), 1493 (m), 1470 (m), 1454 (w), 1410 (w), 1388 (w), 1367 (w), 1263 (w), 1179 (w), 1097 (m), 1014 (m), 825 (s), 771 (w).

HRMS (ESI): calculated for $C_{15}H_{20}Cl$ $[M+H]^+$ 232.1248, found 232.1243.

***R*$_f$** = 0.35 (hexane).



348

8-(4-Chlorophenyl)-1,4-dioxaspiro[4.5]decane (348): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (**319**) (0.242 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a white crystalline solid (113.6 mg, 0.449 mmol, 90%), m.p. 82-84 °C.

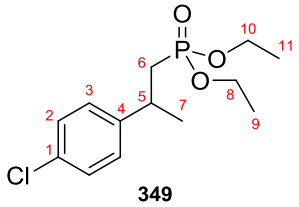
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2 H, H2), 7.16 (d, *J* = 8.5 Hz, 2 H, H3), 3.98 (s, 4 H, H9 and H10), 2.53 (tt, *J* = 12.0, 3.4 Hz, 1 H, H5), 1.89 – 1.80 (m, 4 H, H6a and H7a), 1.80 – 1.71 (m, 2 H, H6b), 1.71 – 1.64 (m, 2 H, H7b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.1 (C4), 131.7 (C1), 128.5 (C2), 128.3 (C3), 108.5 (C8), 64.45 (C9/C10), 64.44 (C9/C10), 42.8 (C5), 35.2 (C7), 31.6 (C6).

FTIR (ν_{max}, cm^{-1}): 2938 (m), 2880 (m), 1493 (m), 1445 (w), 1410 (w), 1371 (w), 1335 (w), 1241 (w), 1172 (w), 1132 (m), 1102 (s), 1035 (m), 1014 (m), 926 (m), 867 (w), 827 (m).

HRMS (ESI): calculated for $C_{14}H_{18}O_2Cl$ $[M+H]^+$ 253.0990, found 253.0991.

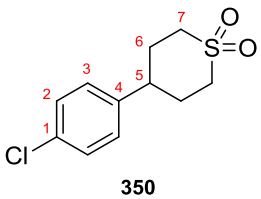
***R*$_f$** = 0.27 (10% EtOAc/hexane).



349

Diethyl (2-(4-chlorophenyl)propyl)phosphonate (349): Following the general procedure for protodeboronative coupling using diethyl ((5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)phosphonate (**320**) (0.280 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 2% MeOH/CH_2Cl_2) provided the title compound as a colourless oil (92.8 mg, 0.319 mmol, 64%). Data are consistent with a reported example.[228]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2 H, H2), 7.14 (d, *J* = 8.5 Hz, 2 H, H3), 4.03 – 3.86 (m, 4 H, H8 and H10), 3.23 – 3.14 (m, 1 H, H5), 2.08 – 1.94 (m, 2 H, H6), 1.34 (d, *J* = 7.0 Hz, 3 H, H7), 1.23 (t, *J* = 7.1 Hz, 3 H, H9/H11), 1.19 (t, *J* = 7.1 Hz, 3 H, H9/H11).
^{13}C NMR (150 MHz, $CDCl_3$): δ 145.2 (d, *J* = 11.4 Hz, C4), 132.1 (C1), 128.7 (C2), 128.2 (C3), 61.5 (d, *J* = 6.6 Hz, C8/C10), 61.4 (d, *J* = 6.5 Hz, C8/C10), 34.4 (d, *J* = 139.0 Hz, C6), 34.3 (d, *J* = 3.6 Hz, C5), 23.7 (d, *J* = 10.1 Hz, C7), 16.5 (d, *J* = 6.1 Hz, C9/C11), 16.4 (d, *J* = 6.1 Hz, C9/C11).
^{31}P NMR (245 MHz, $CDCl_3$): δ 29.6 (s, 1 P, C6-P).
FTIR (ν_{max}, cm^{-1}): 2981 (w), 2906 (w), 1493 (w), 1456 (w), 1411 (w), 1392 (w), 1243 (m), 1163 (w), 1095 (m), 1052 (s), 1023 (s), 955 (s), 826 (m), 789 (m), 759 (w).
HRMS (ESI): calculated for $C_{13}H_{21}O_3PCl$ $[M+H]^+$ 291.0911, found 291.0922.
R_f = 0.12 (2% MeOH/CH_2Cl_2).



350

4-(4-Chlorophenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (350): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene 8,8-dioxide (**325**) (0.234 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 50%

EtOAc/hexane) provided the title compound as a white crystalline solid (73.6 mg, 0.301 mmol, 60%), m.p. 208-210 °C (lit. m.p.[225] 208-209 °C).

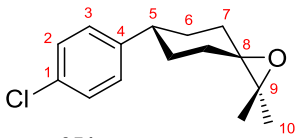
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2 H, H2), 7.16 (d, *J* = 8.4 Hz, 2 H, H3), 3.18 – 3.09 (m, 4 H, H7a and H7b), 2.77 (tt, *J* = 12.3, 3.1 Hz, 1 H, H5), 2.43 – 2.30 (m, 2 H, H6a), 2.23 – 2.14 (m, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.7 (C4), 132.9 (C1), 129.1 (C2), 128.1 (C3), 51.5 (C7), 41.7 (C5), 31.4 (C6).

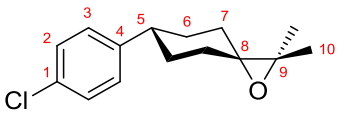
FTIR (ν_{max}, cm^{-1}): 2932 (w), 1495 (m), 1409 (w), 1342 (m), 1287 (s), 1245 (m), 1171 (w), 1122 (s), 1090 (m), 1050 (w), 1013 (w), 987 (w), 950 (w), 896 (w), 853 (w), 825 (m), 797 (w).

HRMS (ESI): calculated for $C_{11}H_{14}O_2SCl$ $[M+H]^+$ 245.0398, found 245.0392.

***R*$_f$** = 0.44 (50% EtOAc/hexane).



351, *diastereomer A*



351, *diastereomer B*

6-(4-Chlorophenyl)-2,2-dimethyl-1-oxaspiro[2.5]octane (351): Following the general procedure for protodeboronative coupling using 9-methoxy-2,2,9-trimethyl-1,10-dioxa-7,8-diazadispiro[2.2.4^6.2^3]dodec-7-ene (**321**) (0.240 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% Et_2O/hexane) provided the title compound as separable diastereomers (1:1) as a white crystalline solids (A: 47.2 mg, 0.188 mmol; B: 54.8 mg, 0.219 mmol; combined yield 81%), m.p. 91-92 °C for diastereomer A and m.p. 80-82 °C for diastereomer B.

Diastereomer A:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.17 (d, *J* = 8.5 Hz, 2 H, H3), 2.62 – 2.53 (m, 1 H, H5), 1.94 – 1.85 (m, 2 H, H6a), 1.85 – 1.74 (m, 4 H, H6b and H7a), 1.75 – 1.64 (m, 2 H, H7b), 1.34 (s, 6 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.4 (C4), 131.8 (C1), 128.6 (C2), 128.3 (C3), 65.1 (C8), 63.0 (C9), 43.2 (C5), 31.6 (C6), 30.3 (C7), 20.7 (C10).

FTIR (ν_{max}, cm^{-1}): 2926 (m), 1493 (s), 1441 (w), 1377 (m), 1274 (w), 1222 (w), 1178 (w), 1126 (m), 1094 (s), 1073 (m), 1013 (m), 970 (w), 926 (w), 880 (w), 862 (m), 827 (s).

HRMS (ESI): calculated for $C_{15}H_{19}OClNa$ $[M+Na]^+$ 273.1017, found 273.1010.

$\boldsymbol{R_f}$ = 0.37 (10% Et_2O/hexane).

Diastereomer B:

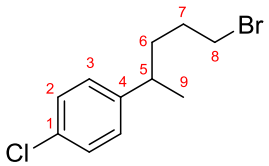
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 2.64 (tt, *J* = 12.1, 3.6 Hz, 1 H, H5), 2.05 – 1.97 (m, 2 H, H6a), 1.85 (td, *J* = 13.4, 3.5 Hz, 2 H, H7a), 1.81 – 1.74 (m, 2 H, H7b), 1.58 – 1.46 (m, 2 H, H6b), 1.40 (s, 6 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7 (C4), 131.9 (C1), 128.6 (C2), 128.2 (C3), 66.3 (C8), 62.5 (C9), 43.2 (C5), 33.6 (C6), 31.5 (C7), 21.0 (C10).

FTIR (ν_{max}, cm^{-1}): 3005 (w), 2979 (w), 2921 (m), 2856 (m), 1492 (m), 1470 (w), 1412 (w), 1377 (m), 1214 (w), 1168 (w), 1120 (m), 1087 (m), 1060 (w), 1015 (m), 985 (w), 896 (w), 857 (m), 821 (s).

HRMS (ESI): calculated for $C_{15}H_{19}OClNa$ $[M+Na]^+$ 273.1017, found 273.1012.

$\boldsymbol{R_f}$ = 0.21 (10% Et_2O/hexane).



352

1-(5-Bromopentan-2-yl)-4-chlorobenzene (352): Following the general procedure for protodeboronative coupling using 2-(3-bromopropyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**326**) (0.251 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as a colourless oil (42.2 mg, 0.161 mmol, 32%).

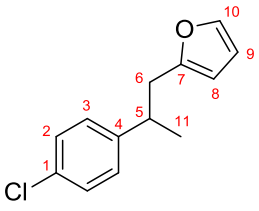
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2 H, H2), 7.11 (d, *J* = 8.4 Hz, 2 H, H3), 3.41 – 3.28 (m, 2 H, H8), 2.74 – 2.65 (m, 1 H, H5), 1.86 – 1.62 (m, 4 H, H6 and H7), 1.25 (d, *J* = 7.0 Hz, 3 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.4 (C4), 131.8 (C1), 128.7 (C2), 128.4 (C3), 39.0 (C5), 36.8 (C6), 33.9 (C8), 31.0 (C7), 22.5 (C9).

FTIR (ν_{max}, cm^{-1}): 2961 (m), 2927 (w), 1596 (w), 1493 (m), 1455 (m), 1411 (w), 1377 (w), 1295 (w), 1245 (w), 1214 (w), 1091 (m), 1013 (m), 946 (w), 824 (s), 787 (w), 769 (w).

HRMS (ESI): calculated for $C_{11}H_{15}BrCl$ $[M+H]^+$ 261.0040, found 261.0045.

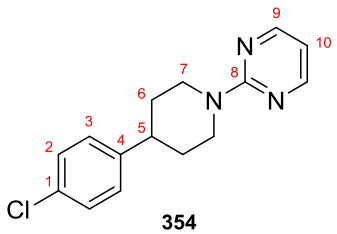
$\boldsymbol{R_f}$ = 0.32 (hexane).



353

2-(2-(4-Chlorophenyl)propyl)furan (353): Following the general procedure for protodeboronative coupling using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**322**) (0.210 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: hexane) provided the title compound as an orange oil (72.0 mg, 0.326 mmol, 65%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 1 H, H10), 7.26 (d, *J* = 8.5 Hz, 2 H, H2), 7.11 (d, *J* = 8.5 Hz, 2 H, H3), 6.24 (dd, *J* = 3.1, 1.9 Hz, 1 H, H9), 5.88 (d, *J* = 3.1 Hz, 1 H, H8), 3.17 – 3.09 (m, 1 H, H5), 2.89 (dd, *J* = 14.9, 7.0 Hz, 1 H, H6a), 2.83 (dd, *J* = 14.9, 7.8 Hz, 1 H, H6b), 1.27 (d, *J* = 7.0 Hz, 3 H, H11).
^{13}C NMR (150 MHz, $CDCl_3$): δ 154.3 (C7), 145.0 (C4), 141.1 (C10), 131.9 (C1), 128.6 (C2), 128.4 (C3), 110.2 (C9), 106.4 (C8), 38.8 (C5), 36.9 (C6), 21.5 (C11).
FTIR (ν_{max}, cm^{-1}): 2964 (w), 2930 (w), 1795 (w), 1597 (w), 1493 (s), 1455 (w), 1411 (w), 1376 (w), 1210 (w), 1146 (m), 1093 (s), 1012 (s), 933 (m), 883 (w), 824 (s), 767 (w).
HRMS (ESI): calculated for $C_{13}H_{14}OCl$ $[M+H]^+$ 221.0728, found 221.0734.
R_f = 0.47 (hexane).



354

2-(4-(4-Chlorophenyl)piperidin-1-yl)pyrimidine (354): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (**323**) (0.263 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a white crystalline solid (77.4 mg, 0.283 mmol, 57%), m.p. 88-90 °C.

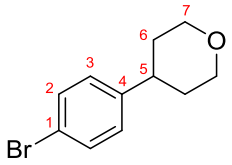
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 4.7 Hz, 2 H, H9), 7.26 (d, *J* = 8.4 Hz, 2 H, H2), 7.14 (d, *J* = 8.4 Hz, 2 H, H3), 6.46 (t, *J* = 4.7 Hz, 1 H, H10), 4.97 – 4.88 (m, 2 H, H7a), 2.94 (td, *J* = 12.7, 2.4 Hz, 2 H, H7b), 2.77 (tt, *J* = 12.7, 3.5 Hz, 1 H, H5), 1.94 – 1.87 (m, 2 H, H6a), 1.65 (qd, *J* = 12.7, 4.2 Hz, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.7 (C8), 157.9 (C9), 144.5 (C4), 132.0 (C1), 128.7 (C2), 128.3 (C3), 109.6 (C10), 44.5 (C7), 42.6 (C5), 33.2 (C6).

FTIR (ν_{max}, cm^{-1}): 3026 (w), 2991 (w), 2934 (w), 2849 (w), 1584 (s), 1545 (m), 1493 (s), 1459 (m), 1446 (m), 1410 (w), 1393 (w), 1361 (s), 1306 (w), 1273 (w), 1239 (w), 1180 (w), 1094 (w), 1012 (w), 979 (m), 947 (w), 827 (w), 796 (m).

HRMS (ESI): calculated for $C_{15}H_{17}N_3Cl$ $[M+H]^+$ 274.1106, found 274.1116.

***R*$_f$** = 0.24 (20% EtOAc/hexane).



355

4-(4-Bromophenyl)tetrahydro-2*H*-pyran (355): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-bromophenylboronic acid (100.4 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a white amorphous solid (82.9 mg, 0.344 mmol, 69%), m.p. 72-74 °C (lit. m.p.[164] 61-62 °C). Data are consistent with a reported example.[164]

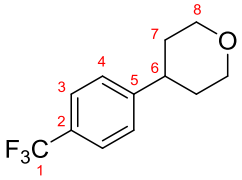
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2 H, H2), 7.10 (d, *J* = 8.4 Hz, 2 H, H3), 4.12 – 4.03 (m, 2 H, H7a), 3.51 (td, *J* = 11.5, 2.8 Hz, 2 H, H7b), 2.72 (tt, *J* = 11.4, 4.5 Hz, 1 H, H5), 1.83 – 1.70 (m, 4 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.9 (C4), 131.7 (C2), 128.6 (C3), 120.1 (C1), 68.4 (C7), 41.2 (C5), 33.9 (C6).

FTIR (ν_{max}, cm^{-1}): 2963 (w), 2939 (m), 2915 (m), 2871 (w), 2841 (m), 1590 (w), 1490 (m), 1440 (w), 1428 (w), 1408 (w), 1383 (m), 1300 (w), 1295 (w), 1263 (w), 1250 (w), 1236 (m), 1199 (w), 1126 (s), 1085 (s), 1075 (m), 1020 (m), 1008 (m), 979 (m), 910 (w), 896 (m), 837 (m), 819 (s).

HRMS (ESI): calculated for $C_{11}H_{14}OBr$ $[M+H]^+$ 241.0223, found 241.0226.

***R*$_f$** = 0.25 (10% EtOAc/hexane).



356

4-(4-(Trifluoromethyl)phenyl)tetrahydro-2*H*-pyran (356): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-(trifluoromethyl)phenylboronic acid (95.0 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (78.0 mg, 0.339 mmol, 68%). Data are consistent with a reported example.[229]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.2 Hz, 2 H, H3), 7.34 (d, *J* = 8.2 Hz, 2 H, H4), 4.16 – 4.04 (m, 2 H, H8a), 3.54 (td, *J* = 11.7, 2.3 Hz, 2 H, H8b), 2.83 (tt, *J* = 11.8, 4.0 Hz, 1 H, H6), 1.91 – 1.72 (m, 4 H, H7).

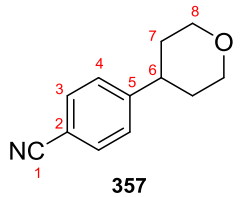
^{13}C NMR (150 MHz, $CDCl_3$): δ 149.9 (C5), 128.8 (q, *J* = 32.3 Hz, C2), 127.2 (C4), 125.6 (q, *J* = 3.8 Hz, C3), 124.4 (q, *J* = 271.8 Hz, C1), 68.3 (C8), 41.6 (C6), 33.8 (C7).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 2939 (w), 2845 (w), 1619 (w), 1468 (w), 1444 (w), 1420 (w), 1387 (w), 1324 (s), 1259 (w), 1239 (w), 1190 (w), 1162 (m), 1116 (s), 1098 (s), 1086 (m), 1068 (s), 1016 (m), 982 (w), 955 (w), 913 (w), 896 (w), 837 (m), 802 (w), 761 (w).

HRMS (ESI): calculated for $C_{12}H_{14}F_3O$ $[M+H]^+$ 231.0991, found 231.0984.

***R*$_f$** = 0.21 (10% EtOAc/hexane).



357

4-(Tetrahydro-2*H*-pyran-4-yl)benzonitrile (357): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-cyanophenylboronic acid (73.5 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a white amorphous solid (52.7 mg, 0.281 mmol, 56%), m.p. 58-60 °C. Compound has been prepared previously,[229] but NMR spectra were recorded in acetone-d_6.

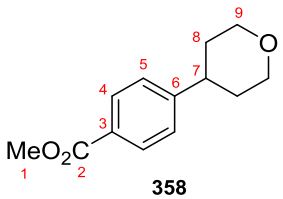
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2 H, H3), 7.31 (d, *J* = 8.3 Hz, 2 H, H4), 4.11 – 4.04 (m, 2 H, H8a), 3.51 (td, *J* = 11.5, 2.7 Hz, 2 H, H8b), 2.81 (tt, *J* = 11.5, 4.4 Hz, 1 H, H6), 1.84 – 1.70 (m, 4 H, H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 151.2 (C5), 132.5 (C3), 127.7 (C4), 119.0 (C1), 110.3 (C2), 68.1 (C8), 41.8 (C6), 33.5 (C7).

FTIR (ν_{max}, cm^{-1}): 2939 (m), 2842 (m), 2226 (m, C≡N), 1608 (m), 1505 (m), 1467 (w), 1443 (m), 1417 (w), 1387 (m), 1292 (w), 1265 (w), 1239 (m), 1200 (w), 1179 (w), 1124 (s), 1100 (m), 1084 (s), 1018 (m), 982 (m), 913 (w), 895 (m), 838 (s), 808 (m).

HRMS (ESI): calculated for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1070, found 188.1086.

***R*$_f$** = 0.22 (20% EtOAc/hexane).



358

Methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate (358): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-methoxycarbonylphenylboronic acid (90.0 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 5% Et_2O/CH_2Cl_2) provided the title compound as a white crystalline solid (63.4 mg, 0.306 mmol, 61%), m.p. 71-72 °C (lit. m.p.[159] 74-75 °C). Data are consistent with a reported example.[159]

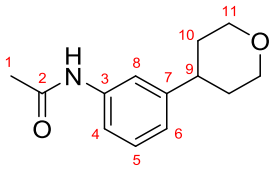
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.3 Hz, 2 H, H4), 7.29 (d, *J* = 8.3 Hz, 2 H, H5), 4.08 (dd, *J* = 11.5, 4.2 Hz, 2 H, H9a), 3.90 (s, 3 H, H1), 3.53 (td, *J* = 11.5, 2.3 Hz, 2 H, H9b), 2.81 (tt, *J* = 11.8, 4.0 Hz, 1 H, H7), 1.88 – 1.73 (m, 4 H, H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 167.1 (C2), 151.2 (C6), 130.0 (C4), 128.4 (C3), 126.9 (C5), 68.3 (C9), 52.1 (C1), 41.8 (C7), 33.7 (C8).

FTIR (ν_{max}, cm^{-1}): 2964 (w), 2933 (w), 2907 (w), 2853 (w), 1719 (s, C=O), 1610 (w), 1573 (w), 1440 (m), 1415 (w), 1390 (w), 1362 (w), 1289 (m), 1278 (m), 1236 (w), 1198 (w), 1180 (w), 1168 (w), 1130 (w), 1110 (m), 1097 (m), 1082 (m), 1018 (m), 978 (w), 962 (w), 915 (w), 894 (w), 858 (w), 842 (w), 825 (w), 764 (m).

HRMS (ESI): calculated for $C_{13}H_{17}O_3$ $[M+H]^+$ 221.1172, found 221.1179.

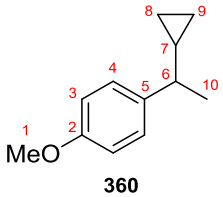
***R*$_f$** = 0.38 (5% Et_2O/CH_2Cl_2).



359

***N*-(3-(Tetrahydro-2*H*-pyran-4-yl)phenyl)acetamide (359):** Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 3-acetamidophenylboronic acid (89.5 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as an off-white amorphous solid (96.9 mg, 0.442 mmol, 88%), m.p. 128-131 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (br s, 1 H, NH), 7.41 (s, 1 H, H8), 7.35 (d, *J* = 8.0 Hz, 1 H, H4), 7.28 – 7.21 (m, 1 H, H5), 6.96 (d, *J* = 7.6 Hz, 1 H, H6), 4.06 (dd, *J* = 11.3, 3.5 Hz, 2 H, H11a), 3.51 (td, *J* = 11.3, 2.4 Hz, 2 H, H11b), 2.73 (tt, *J* = 11.6, 4.2 Hz, 1 H, H9), 2.16 (s, 3 H, H1), 1.85 – 1.70 (m, 4 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6 (C2), 147.0 (C7), 138.3 (C3), 129.2 (C5), 122.7 (C6), 118.4 (C8), 118.0 (C4), 68.4 (C11), 41.6 (C9), 34.0 (C10), 24.7 (C1).
FTIR (ν_{max}, cm^{-1}): 3290 (w, NH), 2938 (m), 2845 (m), 1668 (s, C=O), 1611 (s), 1594 (m), 1555 (s), 1490 (m), 1442 (m), 1372 (m), 1303 (m), 1259 (m), 1238 (m), 1130 (m), 1084 (m), 1015 (m), 980 (w), 917 (w), 869 (w), 824 (w), 791 (w).
HRMS (ESI): calculated for $C_{13}H_{18}NO_2$ $[M+H]^+$ 220.1332, found 220.1328.
***R*$_f$** = 0.27 (5% MeOH/CH_2Cl_2).



360

1-(1-Cyclopropylethyl)-4-methoxybenzene (360): Following a modified version of the general procedure for protodeboronative coupling using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**316**) (0.236 g, 1.0 mmol) and 4-methoxyphenylboronic acid (76.0 mg, 0.5 mmol) – the output of the reactor was heated in the sealed vial at 75 °C for 16 h. Purification by silica gel column chromatography (eluent: 2% EtOAc/hexane) provided the title compound as a colourless oil (49.0 mg, 0.278 mmol, 56%).

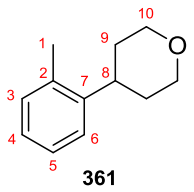
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.6 Hz, 2 H, H4), 6.87 (d, *J* = 8.6 Hz, 2 H, H3), 3.81 (s, 3 H, H1), 2.02 – 1.92 (m, 1 H, H6), 1.33 (d, *J* = 7.1 Hz, 3 H, H10), 0.97 – 0.87 (m, 1 H, H7), 0.59 – 0.51 (m, 1 H, H8a), 0.48 – 0.40 (m, 1 H, H9a), 0.24 – 0.12 (m, 2 H, H8b and H9b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.9 (C2), 139.6 (C5), 127.9 (C4), 113.7 (C3), 55.4 (C1), 43.8 (C6), 21.8 (C10), 18.9 (C7), 4.7 (C8/C9), 4.4 (C8/C9).

FTIR (ν_{max}, cm^{-1}): 3076 (w), 2998 (w), 2959 (w), 2934 (w), 2835 (w), 1612 (w), 1584 (w), 1510 (s), 1455 (w), 1442 (w), 1428 (w), 1369 (w), 1333 (w), 1303 (w), 1288 (w), 1268 (w), 1241 (s), 1178 (m), 1111 (w), 1073 (w), 1030 (m), 1015 (m), 972 (w), 925 (w), 830 (m), 806 (m), 769 (w).

HRMS (ESI): calculated for $C_{12}H_{17}O$ $[M+H]^+$ 177.1274, found 177.1266.

***R*$_f$** = 0.37 (2% EtOAc/hexane).



361

4-(*o*-Tolyl)tetrahydro-2*H*-pyran (361): Following a modified version of the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and *o*-tolylboronic acid (68.0 mg, 0.5 mmol) – the output of the reactor was heated in the sealed vial at 75 °C for 16 h. Purification by silica gel column chromatography (eluent: 5% EtOAc/hexane) provided the title compound as a colourless oil (60.9 mg, 0.346 mmol, 69%). Data are consistent with a reported example.[229]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 2 H, H5 and H6), 7.18 (d, *J* = 6.9 Hz, 1 H, H3), 7.15 – 7.11 (m, 1 H, H4), 4.12 (dd, *J* = 11.8, 4.4 Hz, 2 H, H10a), 3.58 (td, *J* = 11.8, 1.9 Hz, 2 H, H10b), 3.00 (tt, *J* = 12.0, 3.6 Hz, 1 H, H8), 2.38 (s, 3 H, H1), 1.90 – 1.80 (m, 2 H, H9a), 1.74 – 1.67 (m, 2 H, H9b).

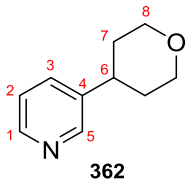
^{13}C NMR (150 MHz, $CDCl_3$): δ 143.8 (C7), 135.2 (C2), 130.5 (C3), 126.5 (C5), 126.1 (C4), 125.6 (C6), 68.8 (C10), 37.5 (C8), 33.3 (C9), 19.4 (C1).

FTIR (ν_{max}, cm^{-1}): 3020 (w), 2944 (m), 2840 (m), 1605 (w), 1493 (m), 1462 (m), 1442 (w), 1386 (m), 1367 (w), 1297 (w), 1257 (w), 1235 (m), 1217 (w), 1173 (w), 1132 (m), 1121 (m),

1091 (m), 1052 (w), 1021 (m), 1011 (m), 980 (m), 940 (w), 895 (m), 834 (m), 809 (w), 779 (w), 750 (s).

HRMS (ESI): calculated for $C_{12}H_{17}O$ $[M+H]^+$ 177.1274, found 177.1277.

$\boldsymbol{R_f}$ = 0.22 (5% EtOAc/hexane).



362

3-(Tetrahydro-2*H*-pyran-4-yl)pyridine (362): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 3-pyridinylboronic acid (61.5 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 5% MeOH/CH_2Cl_2) provided the title compound as a yellow oil (24.6 mg, 0.151 mmol, 30%). Compound has been prepared previously,[229] but NMR spectra were recorded in acetone-d_6.

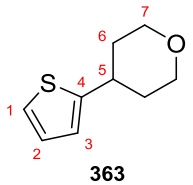
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (br s, 1 H, H5), 8.47 (d, *J* = 3.9 Hz, 1 H, H1), 7.55 (dt, *J* = 7.9, 1.8 Hz, 1 H, H3), 7.28 – 7.24 (m, 1 H, H2), 4.12 – 4.07 (m, 2 H, H8a), 3.54 (td, *J* = 11.7, 2.4 Hz, 2 H, H8b), 2.80 (tt, *J* = 11.8, 4.2 Hz, 1 H, H6), 1.87 – 1.74 (m, 4 H, H7).

^{13}C NMR (150 MHz, $CDCl_3$): δ 148.9 (C5), 147.9 (C1), 141.0 (C4), 134.3 (C3), 123.7 (C2), 68.3 (C8), 39.2 (C6), 33.7 (C7).

FTIR (ν_{max}, cm^{-1}): 2938 (m), 2846 (m), 1576 (w), 1480 (w), 1443 (w), 1426 (m), 1388 (m), 1275 (w), 1263 (w), 1239 (m), 1182 (w), 1126 (s), 1098 (m), 1085 (s), 1050 (w), 1020 (s), 982 (m), 895 (m), 840 (m), 812 (w).

HRMS (ESI): calculated for $C_{10}H_{14}NO$ $[M+H]^+$ 164.1070, found 164.1062.

$\boldsymbol{R_f}$ = 0.37 (5% MeOH/CH_2Cl_2).



363

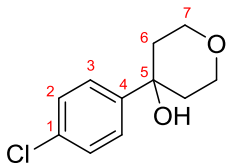
4-(Thiophen-2-yl)tetrahydro-2*H*-pyran (363): Following the general procedure for protodeboronative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 2-thienylboronic acid (64.0 mg, 0.5 mmol), purified by

silica gel column chromatography (eluent: 30% CH_2Cl_2/hexane) provided the title compound as a colourless oil (32.3 mg, 0.192 mmol, 38%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 5.1, 1.1 Hz, 1 H, H1), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1 H, H2), 6.85 – 6.82 (m, 1 H, H3), 4.08 – 4.02 (m, 2 H, H7a), 3.52 (td, *J* = 11.8, 2.1 Hz, 2 H, H7b), 3.07 (tt, *J* = 11.8, 3.9 Hz, 1 H, H5), 1.97 – 1.92 (m, 2 H, H6a), 1.87 – 1.79 (m, 2 H, H6b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 150.2 (C4), 126.8 (C2), 122.8 (C1), 122.3 (C3), 68.1 (C7), 36.7 (C5), 35.1 (C6).
FTIR (ν_{max}, cm^{-1}): 2937 (m), 2842 (m), 1533 (w), 1466 (w), 1442 (m), 1387 (m), 1311 (w), 1257 (m), 1240 (m), 1125 (s), 1088 (s), 1015 (m), 981 (m), 879 (m), 852 (m), 821 (m).
HRMS (ESI): calculated for $C_9H_{13}OS$ $[M+H]^+$ 169.0682, found 169.0682.
R_f = 0.24 (30% CH_2Cl_2/hexane).

5.4.3. Synthetic procedures and characterisation for oxidative cross-couplings

General procedure for oxidative coupling: A solution of the appropriate oxadiazoline (1.0 mmol, 2 equiv.), boronic acid (0.5 mmol, 1.0 equiv.) and DIPEA (0.17 mL, 1.0 mmol, 2 equiv.) in CH_2Cl_2 (10 mL) was pumped at a flow rate of 0.125 mL min^{-1} through a Vapourtec UV-150 photochemical reactor (10 mL reactor volume, FEP tubing) held at 10 °C and the reactor output was monitored using a FlowIR® device (SiComp head, 2100-2000 cm^{-1} and 1750-1700 cm^{-1}). After 80 min once the reaction mixture has fully been taken up by the pump, the input was swapped to CH_2Cl_2 solvent. When the FlowIR® showed that the reaction plug was exiting the output stream (by monitoring the MeOAc C=O stretch at 1750-1700 cm^{-1}), the reaction plug was directed into a round-bottomed flask and stirred for 16 h under air. The mixture was then evaporated under reduced pressure and the residue purified by silica gel column chromatography.



331

4-(4-Chlorophenyl)tetrahydro-2*H*-pyran-4-ol (331): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a white crystalline solid (80.6 mg, 0.378 mmol, 76%), m.p. 69-71 °C (lit. m.p.[230] 77-78 °C). Data are consistent with a reported example.[230]

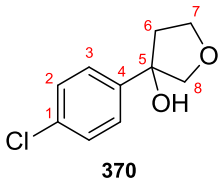
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2 H, H2), 7.33 (d, *J* = 8.8 Hz, 2 H, H3), 3.89 (td, *J* = 11.8, 2.1 Hz, 2 H, H7a), 3.86 – 3.81 (m, 2 H, H7b), 2.14 – 2.06 (m, 2 H, H6a), 1.99 (br s, 1 H, OH), 1.67 – 1.60 (m, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.8 (C4), 133.1 (C1), 128.7 (C3), 126.1 (C2), 70.5 (C5), 63.9 (C7), 38.8 (C6).

FTIR (ν_{max}, cm^{-1}): 3399 (br m, OH), 2955 (m), 2871 (m), 1595 (w), 1494 (m), 1467 (w), 1388 (m), 1302 (w), 1238 (m), 1222 (w), 1125 (m), 1095 (s), 1033 (m), 1013 (s), 965 (w), 915 (w), 826 (s), 798 (w).

HRMS (ESI): calculated for $C_{11}H_{13}O_2ClNa$ $[M+Na]^+$ 235.0496, found 235.0505.

$\boldsymbol{R_f}$ = 0.28 (40% EtOAc/hexane).



370

3-(4-Chlorophenyl)tetrahydrofuran-3-ol (370): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,7-dioxa-1,2-diazaspiro[4.4]non-1-ene (**304**) (0.172 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a colourless oil (57.0 mg, 0.287 mmol, 57%).

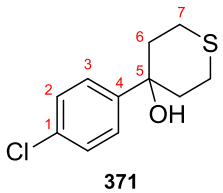
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 2 H, H2), 7.33 (d, *J* = 8.6 Hz, 2 H, H3), 4.19 (td, *J* = 8.8, 7.0 Hz, 1 H, H7a), 4.10 (td, *J* = 8.8, 3.5 Hz, 1 H, H7b), 3.93 (dd, *J* = 9.5, 1.3 Hz, 1 H, H8a), 3.84 (d, *J* = 9.5 Hz, 1 H, H8b), 2.56 (br s, 1 H, OH), 2.37 (dt, *J* = 13.1, 8.8 Hz, 1 H, H6a), 2.24 (dddd, *J* = 13.1, 7.0, 3.5, 1.3 Hz, 1 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 140.9 (C4), 133.5 (C1), 128.7 (C3), 126.9 (C2), 81.6 (C5), 80.5 (C8), 68.1 (C7), 42.2 (C6).

FTIR (ν_{max}, cm^{-1}): 3386 (br m, OH), 2955 (w), 2882 (w), 1599 (w), 1493 (m), 1440 (w), 1400 (w), 1359 (w), 1252 (w), 1136 (m), 1094 (s), 1057 (s), 1013 (s), 976 (m), 923 (m), 892 (m), 823 (s), 775 (m).

HRMS (ESI): calculated for $C_{10}H_{11}O_2ClNa$ $[M+Na]^+$ 221.0340, found 221.0334.

$\boldsymbol{R_f}$ = 0.28 (40% EtOAc/hexane).



371

4-(4-Chlorophenyl)tetrahydro-2*H*-thiopyran-4-ol (371): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (**305**) (0.202 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% Et_2O/hexane) provided the title

compound as an off-white crystalline solid (95.2 mg, 0.416 mmol, 83%), m.p. 88-90 °C (lit. m.p.[230] 86-87 °C). Data are consistent with a reported example.[230]

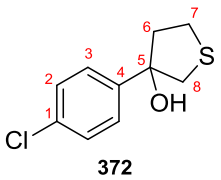
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2 H, H2), 7.32 (d, *J* = 8.7 Hz, 2 H, H3), 3.24 – 3.12 (m, 2 H, H7a), 2.51 – 2.42 (m, 2 H, H7b), 2.18 – 2.08 (m, 2 H, H6a), 2.02 – 1.94 (m, 2 H, H6b), 1.60 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.7 (C4), 133.0 (C1), 128.6 (C3), 125.9 (C2), 71.9 (C5), 39.6 (C6), 24.2 (C7).

FTIR (ν_{max}, cm^{-1}): 3428 (br m, OH), 2916 (m), 1596 (w), 1494 (s), 1424 (m), 1399 (w), 1304 (w), 1275 (m), 1227 (m), 1179 (w), 1136 (w), 1095 (s), 1067 (s), 1027 (w), 1013 (s), 968 (s), 927 (s), 881 (w), 827 (s), 777 (w).

HRMS (ESI): calculated for $C_{11}H_{13}OSClNa$ $[M+Na]^+$ 251.0268, found 251.0270.

R_f = 0.22 (30% Et_2O/hexane).



372

3-(4-Chlorophenyl)tetrahydrothiophen-3-ol (372): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (**306**) (0.188 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% Et_2O/hexane) provided the title compound as a colourless oil (62.6 mg, 0.292 mmol, 58%).

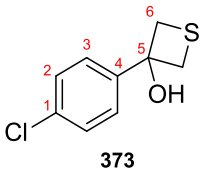
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.6 Hz, 2 H, H2), 7.33 (d, *J* = 8.6 Hz, 2 H, H3), 3.20 (d, *J* = 11.6 Hz, 1 H, H8a), 3.13 (td, *J* = 10.5, 7.0 Hz, 1 H, H7a), 3.05 (ddd, *J* = 10.5, 7.7, 2.5 Hz, 1 H, H7b), 2.96 (dd, *J* = 11.6, 1.4 Hz, 1 H, H8b), 2.71 (br s, 1 H, OH), 2.33 – 2.23 (m, 2 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.1 (C4), 133.5 (C1), 128.6 (C3), 126.8 (C2), 83.5 (C5), 45.5 (C8), 43.4 (C6), 29.0 (C7).

FTIR (ν_{max}, cm^{-1}): 3418 (br w, OH), 2938 (w), 1706 (w), 1596 (w), 1493 (m), 1427 (w), 1400 (m), 1358 (m), 1269 (w), 1208 (m), 1176 (w), 1093 (s), 1065 (w), 1035 (s), 1013 (s), 984 (w), 957 (m), 935 (m), 822 (s).

HRMS (ESI): calculated for $C_{10}H_{11}OSClNa$ $[M+Na]^+$ 237.0111, found 237.0110.

$\boldsymbol{R_f}$ = 0.29 (30% Et_2O/hexane).



373

3-(4-Chlorophenyl)thietan-3-ol (373): Following the general procedure for oxidative coupling using 7-methoxy-7-methyl-8-oxa-2-thia-5,6-diazaspiro[3.4]oct-5-ene (**307**) (0.174 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a yellow oil (20.0 mg, 0.100 mmol, 20%).

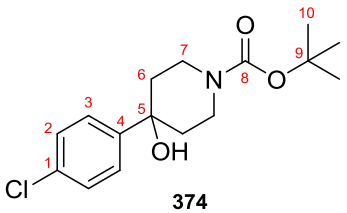
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.6 Hz, 2 H, H2), 7.38 (d, *J* = 8.6 Hz, 2 H, H3), 3.59 (s, 4 H, H6), 2.86 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.1 (C4), 134.0 (C1), 128.9 (C3), 125.9 (C2), 78.8 (C5), 42.8 (C6).

FTIR (ν_{max}, cm^{-1}): 3365 (br w, OH), 2987 (w), 2939 (w), 2850 (w), 1682 (w), 1598 (w), 1575 (w), 1491 (m), 1426 (w), 1400 (w), 1368 (w), 1304 (w), 1265 (w), 1212 (m), 1175 (m), 1127 (w), 1092 (m), 1053 (m), 1013 (m), 954 (m), 880 (w), 826 (s), 771 (w).

HRMS (ESI): calculated for $C_9H_9OSClNa$ $[M+Na]^+$ 222.9955, found 222.9948.

$\boldsymbol{R_f}$ = 0.21 (10% EtOAc/hexane).



374

***tert*-Butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (374):** Following the general procedure for oxidative coupling using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (**308**) (0.285 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% → 30% EtOAc/hexane) provided the title compound as a colourless gum (125.1 mg, 0.401 mmol, 80%).

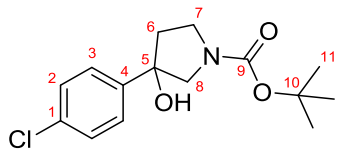
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2 H, H2), 7.31 (d, *J* = 8.7 Hz, 2 H, H3), 3.99 (br s, 2 H, H7a), 3.20 (br s, 2 H, H7b), 2.02 (br s, 1 H, OH), 1.93 (br s, 2 H, H6a), 1.72 – 1.66 (m, 2 H, H6b), 1.46 (s, 9 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.0 (C8), 146.8 (C4), 133.1 (C1), 128.6 (C3), 126.2 (C2), 79.8 (C9), 71.4 (C5), 40.7 – 38.9 (br, C7), 38.5 – 37.6 (br, C6), 28.6 (C10).

FTIR (ν_{max}, cm^{-1}): 3431 (br w, OH), 2975 (w), 2927 (w), 1662 (s, C=O), 1479 (m), 1425 (m), 1392 (m), 1366 (m), 1319 (w), 1277 (m), 1248 (m), 1216 (m), 1163 (s), 1138 (m), 1093 (m), 1029 (m), 1013 (m), 958 (w), 909 (m), 861 (m), 824 (m), 795 (w), 769 (m).

HRMS (ESI): calculated for $C_{16}H_{22}NO_3ClNa$ $[M+Na]^+$ 334.1180, found 334.1193.

***R*$_f$** = 0.14 (20% EtOAc/hexane).



375

***tert*-Butyl 3-(4-chlorophenyl)-3-hydroxypyrrolidine-1-carboxylate (375):** Following the general procedure for oxidative coupling using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,7-triazaspiro[4.4]non-1-ene-7-carboxylate (**309**) (0.271 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 60% Et_2O/hexane) provided the title compound as a colourless gum (82.2 mg, 0.276 mmol, 55%).

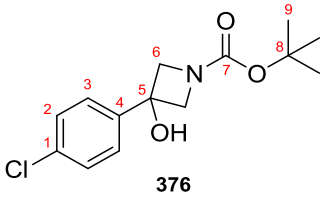
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 and 7.39 (two d from rotamers, *J* = 8.6 Hz, 2 H, H2), 7.31 (two superimposed d from rotamers, *J* = 8.6 Hz, 2 H, H3), 3.72 – 3.45 (m, 4 H, H7 and H8), 2.90 and 2.88 (two br s from rotamers, 1 H, OH), 2.31 – 2.07 (m, 2 H, H6), 1.44 and 1.43 (two s from rotamers, 9 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.9 and 154.7 (rotameric, C9), 141.7 and 141.6 (rotameric, C4), 133.6 (C1), 128.7 (C3), 126.9 (C2), 80.2 and 79.4 (C5), 79.8 (C10), 59.7 and 58.9 (C8), 45.2 and 44.7 (C7), 39.9 and 39.0 (C6), 28.6 (C11).

FTIR (ν_{max}, cm^{-1}): 3405 (br w, OH), 2978 (w), 2892 (w), 1668 (s, C=O), 1493 (w), 1478 (w), 1416 (s), 1367 (m), 1254 (w), 1170 (m), 1136 (s), 1094 (m), 1015 (w), 924 (w), 878 (w), 827 (m), 757 (w).

HRMS (ESI): calculated for $C_{15}H_{20}NO_3ClNa$ $[M+Na]^+$ 320.1024, found 320.1025.

***R*$_f$** = 0.27 (60% Et_2O/hexane).



376

***tert*-Butyl 3-(4-chlorophenyl)-3-hydroxyazetidine-1-carboxylate (376):** Following the general procedure for oxidative coupling using *tert*-butyl 7-methoxy-7-methyl-8-oxa-2,5,6-triazaspiro[3.4]oct-5-ene-2-carboxylate (**310**) (0.257 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) provided the title compound as a white amorphous solid (60.3 mg, 0.213 mmol, 43%), m.p. 128-131 °C (lit. m.p.[231] 139.0-140.6 °C). Data are consistent with a reported example.[231]

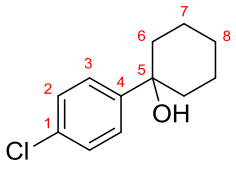
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2 H, H2), 7.34 (d, *J* = 8.7 Hz, 2 H, H3), 4.15 (s, 4 H, H6), 3.65 (br s, 1 H, OH), 1.44 (s, 9 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.6 (C7), 142.1 (C4), 133.7 (C1), 128.8 (C3), 126.2 (C2), 80.3 (C8), 70.8 (C5), 65.5 – 63.5 (br, C6), 28.5 (C9).

FTIR (ν_{max}, cm^{-1}): 3372 (br w, OH), 2978 (w), 2882 (w), 1675 (s, C=O), 1493 (m), 1478 (m), 1416 (s), 1367 (s), 1250 (m), 1160 (s), 1119 (m), 1094 (m), 1013 (m), 936 (w), 860 (w), 826 (w), 772 (w).

HRMS (ESI): calculated for $C_{14}H_{18}NO_3ClNa$ $[M+Na]^+$ 306.0867, found 306.0855.

***R*$_f$** = 0.38 (30% EtOAc/hexane).



377

1-(4-Chlorophenyl)cyclohexan-1-ol (377): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.5]dec-1-ene (**311**) (0.184 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a white crystalline solid (82.2 mg, 0.390 mmol, 78%), m.p. 74-76 °C (lit. m.p.[232] 77 °C). Data are consistent with a reported example.[233]

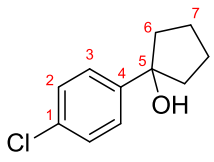
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2 H, H2), 7.30 (d, *J* = 8.7 Hz, 2 H, H3), 1.82 – 1.72 (m, 7 H, H6, H7a and H8a), 1.69 (br s, 1 H, OH), 1.67 – 1.60 (m, 2 H, H7b), 1.36 – 1.21 (m, 1 H, H8b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 148.1 (C4), 132.5 (C1), 128.4 (C3), 126.3 (C2), 73.0 (C5), 38.9 (C6), 25.5 (C8), 22.2 (C7).

FTIR (ν_{max}, cm^{-1}): 3380 (br m, OH), 2933 (s), 2857 (m), 1595 (w), 1494 (m), 1448 (m), 1399 (w), 1257 (w), 1209 (w), 1174 (w), 1134 (w), 1095 (m), 1011 (m), 973 (m), 903 (w), 849 (w), 821 (s).

HRMS (ESI): calculated for $C_{12}H_{15}OClNa$ $[M+Na]^+$ 233.0704, found 233.0700.

***R*$_f$** = 0.24 (10% EtOAc/hexane).



378

1-(4-Chlorophenyl)cyclopentan-1-ol (378): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4-oxa-1,2-diazaspiro[4.5]dec-1-ene (**312**) (0.184 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (63.5 mg, 0.323 mmol, 65%).

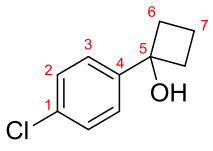
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 2 H, H2), 7.30 (d, *J* = 8.6 Hz, 2 H, H3), 2.03 – 1.92 (m, 6 H, H6 and H7a), 1.88 – 1.78 (m, 2 H, H7b), 1.68 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.7 (C4), 132.6 (C1), 128.4 (C3), 126.7 (C2), 83.2 (C5), 42.1 (C6), 24.0 (C7).

FTIR (ν_{max}, cm^{-1}): 3365 (br w, OH), 2964 (m), 2874 (w), 1597 (w), 1492 (m), 1450 (w), 1399 (w), 1323 (w), 1295 (w), 1178 (w), 1093 (s), 1039 (w), 1012 (s), 1003 (s), 960 (w), 904 (w), 882 (w), 824 (s).

HRMS (ESI): calculated for $C_{11}H_{13}OClNa$ $[M+Na]^+$ 219.0547, found 219.0554.

***R*$_f$** = 0.21 (10% EtOAc/hexane).



379

1-(4-Chlorophenyl)cyclobutan-1-ol (379): Following the general procedure for oxidative coupling using 7-methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (**313**) (0.156 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a colourless oil (60.9 mg, 0.333 mmol, 67%). Data are consistent with a reported example.[234]

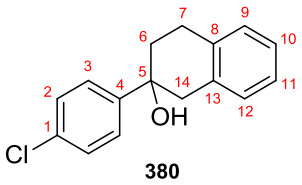
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.6 Hz, 2 H, H2), 7.33 (d, *J* = 8.6 Hz, 2 H, H3), 2.55 – 2.48 (m, 2 H, H6a), 2.39 – 2.32 (m, 2 H, H6b), 2.14 (br s, 1 H, OH), 2.06 – 1.98 (m, 1 H, H7a), 1.73 – 1.64 (m, 1 H, H7b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.9 (C4), 133.1 (C1), 128.6 (C3), 126.6 (C2), 76.7 (C5), 37.1 (C6), 13.0 (C7).

FTIR (ν_{max}, cm^{-1}): 3341 (br w, OH), 2988 (w), 2940 (w), 1599 (w), 1493 (m), 1423 (w), 1399 (w), 1282 (w), 1244 (m), 1181 (w), 1133 (m), 1093 (s), 1067 (w), 1032 (w), 1012 (s), 957 (w), 890 (w), 828 (s).

HRMS (ESI): calculated for $C_{10}H_{11}OClNa$ $[M+Na]^+$ 205.0391, found 205.0400.

R_f = 0.29 (20% EtOAc/hexane).



380

2-(4-Chlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-ol (380): Following the general procedure for oxidative coupling using 5'-methoxy-5'-methyl-3,4-dihydro-1*H*,5'*H*-spiro[naphthalene-2,2'-[1,3,4]oxadiazole] (**314**) (0.232 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% Et_2O/hexane) provided the title compound as a colourless gum (92.3 mg, 0.357 mmol, 71%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.6 Hz, 2 H, H2), 7.33 (d, *J* = 8.6 Hz, 2 H, H3), 7.21 – 7.08 (m, 4 H, H9, H10, H11 and H12), 3.29 (d, *J* = 16.9 Hz, 1 H, H14a), 3.15 – 3.05

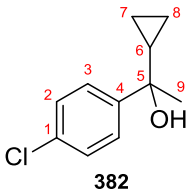
(m, 1 H, H7a), 3.01 (d, *J* = 16.9 Hz, 1 H, H14b), 2.79 (dt, *J* = 17.1, 5.3 Hz, 1 H, H7b), 2.27 – 2.18 (m, 1 H, H6a), 2.11 – 2.04 (m, 1 H, H6b), 2.01 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.3 (C4), 135.3 (C8/C13), 134.2 (C8/C13), 133.0 (C1), 129.5 (C9/C10/C11/C12), 129.0 (C9/C10/C11/C12), 128.5 (C3), 126.5 (C2), 126.4 (C9/C10/C11/C12), 126.2 (C9/C10/C11/C12), 72.4 (C5), 43.8 (C14), 35.5 (C6), 26.4 (C7).

FTIR (ν_{max}, cm^{-1}): 3367 (br w, OH), 3061 (w), 3019 (w), 2921 (w), 2845 (w), 1596 (w), 1583 (w), 1494 (m), 1453 (w), 1433 (w), 1398 (w), 1346 (w), 1317 (w), 1298 (w), 1243 (w), 1175 (w), 1092 (m), 1077 (m), 1037 (w), 1013 (m), 964 (m), 908 (m), 876 (w), 853 (w), 816 (s), 762 (m).

HRMS (ESI): calculated for $C_{16}H_{15}OClNa$ $[M+Na]^+$ 281.0704, found 281.0713.

***R*$_f$** = 0.31 (30% Et_2O/hexane).



382

1-(4-Chlorophenyl)-1-cyclopropylethan-1-ol (382): Following the general procedure for oxidative coupling using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**316**) (0.170 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (82.8 mg, 0.421 mmol, 84%). Data are consistent with a reported example.[235]

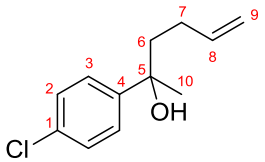
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.6 Hz, 2 H, H2), 7.30 (d, *J* = 8.6 Hz, 2 H, H3), 1.63 (br s, 1 H, OH), 1.46 (s, 3 H, H9), 1.22 (tt, *J* = 8.3, 5.6 Hz, 1 H, H6), 0.58 – 0.49 (m, 1 H, H7a), 0.49 – 0.35 (m, 3 H, H7b and H8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.7 (C4), 132.6 (C1), 128.2 (C3), 126.8 (C2), 73.1 (C5), 28.6 (C9), 23.0 (C6), 2.2 (C7/C8), 1.2 (C7/C8).

FTIR (ν_{max}, cm^{-1}): 3419 (br w, OH), 3085 (w), 3009 (w), 2978 (w), 1597 (w), 1489 (m), 1455 (w), 1400 (w), 1368 (w), 1227 (w), 1175 (w), 1091 (s), 1043 (m), 1012 (s), 952 (w), 925 (m), 897 (m), 828 (s).

HRMS (ESI): calculated for $C_{11}H_{13}OClNa$ $[M+Na]^+$ 219.0547, found 219.0546.

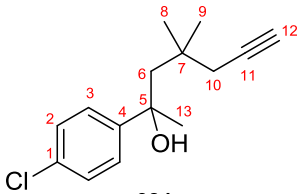
***R*$_f$** = 0.23 (10% EtOAc/hexane).



383

2-(4-Chlorophenyl)hex-5-en-2-ol (383): Following the general procedure for oxidative coupling using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**317**) (0.184 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (97.5 mg, 0.463 mmol, 93%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.6 Hz, 2 H, H2), 7.30 (d, *J* = 8.6 Hz, 2 H, H3), 5.84 – 5.72 (m, 1 H, H8), 5.00 – 4.94 (m, 1 H, $H9_{trans}$), 4.93 (d, *J* = 10.3 Hz, 1 H, $H9_{cis}$), 2.10 – 1.97 (m, 1 H, H7a), 1.95 – 1.84 (m, 4 H, H6, H7b and OH), 1.54 (s, 3 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 146.3 (C4), 138.6 (C8), 132.5 (C1), 128.4 (C3), 126.5 (C2), 114.9 (C9), 74.6 (C5), 43.1 (C6), 30.5 (C10), 28.6 (C7).
FTIR (ν_{max}, cm^{-1}): 3406 (br w, OH), 2976 (w), 2930 (w), 1641 (w), 1598 (w), 1490 (m), 1452 (w), 1397 (w), 1373 (w), 1304 (w), 1219 (w), 1093 (s), 1013 (s), 996 (w), 934 (w), 910 (m), 881 (w), 829 (s).
HRMS (ESI): calculated for $C_{12}H_{15}OClNa$ $[M+Na]^+$ 233.0704, found 233.0699.
***R*$_f$** = 0.26 (10% EtOAc/hexane).



384

2-(4-Chlorophenyl)-4,4-dimethylhept-6-yn-2-ol (384): Following the general procedure for oxidative coupling using 2-(2,2-dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**318**) (0.224 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/hexane) provided the title compound as a colourless oil (104.4 mg, 0.416 mmol, 83%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2 H, H2), 7.28 (d, *J* = 8.7 Hz, 2 H, H3), 2.20 (dd, *J* = 16.5, 2.7 Hz, 1 H, H10a), 2.04 (t, *J* = 2.7 Hz, 1 H, H12), 1.99 (s, 2 H, H6), 1.943

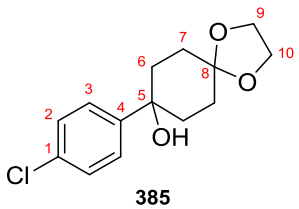
(br s, 1 H, OH), 1.940 (dd, *J* = 16.5, 2.7 Hz, 1 H, H10b), 1.54 (s, 3 H, H13), 0.87 (s, 3 H, H8/H9), 0.76 (s, 3 H, H8/H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.8 (C4), 132.2 (C1), 128.2 (C3), 126.6 (C2), 83.3 (C11), 75.2 (C5), 70.9 (C12), 52.6 (C6), 34.9 (C13), 34.5 (C7), 32.8 (C10), 29.4 (C8/C9), 28.7 (C8/C9).

FTIR (ν_{max}, cm^{-1}): 3429 (br w, OH), 3304 (w, alkyne CH), 2961 (w), 2927 (w), 1598 (w), 1491 (m), 1471 (w), 1425 (w), 1398 (w), 1367 (w), 1265 (w), 1174 (w), 1093 (m), 1075 (m), 1013 (s), 946 (w), 923 (w), 829 (s).

HRMS (ESI): calculated for $C_{15}H_{19}OClNa$ $[M+Na]^+$ 273.1017, found 273.1020.

***R*$_f$** = 0.28 (10% EtOAc/hexane).



385

8-(4-Chlorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (385): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (**319**) (0.242 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% EtOAc/CH_2Cl_2) provided the title compound as a white crystalline solid (111.1 mg, 0.413 mmol, 83%), m.p. 158-160 °C (lit m.p.[236] 147-149 °C). Data are consistent with a reported example.[237]

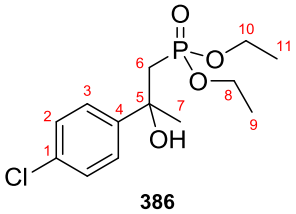
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.6 Hz, 2 H, H2), 7.30 (d, *J* = 8.6 Hz, 2 H, H3), 4.02 – 3.93 (m, 4 H, H9/H10), 2.17 – 2.04 (m, 4 H, H6a and H7a), 1.81 – 1.75 (m, 2 H, H6b), 1.72 – 1.66 (m, 2 H, H7b), 1.64 (br s, 1 H, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.2 (C4), 132.8 (C1), 128.5 (C3), 126.2 (C2), 108.4 (C8), 72.4 (C5), 64.5 (C9/C10), 64.4 (C9/C10), 36.7 (C6), 30.8 (C7).

FTIR (ν_{max}, cm^{-1}): 3459 (br w, OH), 2931 (m), 2884 (w), 1493 (m), 1435 (w), 1398 (w), 1369 (w), 1251 (w), 1216 (w), 1181 (w), 1145 (w), 1096 (s), 1034 (m), 1013 (m), 987 (m), 943 (m), 889 (w), 826 (m), 772 (w).

HRMS (ESI): calculated for $C_{14}H_{17}O_3ClNa$ $[M+Na]^+$ 291.0758, found 291.0768.

***R*$_f$** = 0.23 (10% EtOAc/CH_2Cl_2).



386

Diethyl (2-(4-chlorophenyl)-2-hydroxypropyl)phosphonate (386): Following the general procedure for oxidative coupling using diethyl ((5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)phosphonate (**320**) (0.280 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 35% EtOAc/60% hexane/5% MeOH) provided the title compound as a colourless oil (92.6 mg, 0.302 mmol, 60%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 2 H, H2), 7.29 (d, *J* = 8.6 Hz, 2 H, H3), 5.03 (s, 1 H, OH), 4.13 – 3.96 (m, 2 H, H8/H10), 3.79 – 3.69 (m, 1 H, H8/H10), 3.55 – 3.46 (m, 1 H, H8/H10), 2.40 (dd, *J* = 17.5, 15.5 Hz, 1 H, H6a), 2.29 (t, *J* = 16.5, 15.5 Hz, 1 H, H6b), 1.58 (d, *J* = 2.1 Hz, 3 H, H7), 1.30 (t, *J* = 7.1 Hz, 3 H, H9/H11), 1.02 (t, *J* = 7.1 Hz, 3 H, H9/H11).

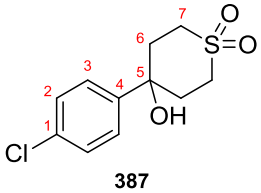
^{13}C NMR (150 MHz, $CDCl_3$): δ 145.9 (d, *J* = 7.3 Hz, C4), 132.7 (C1), 128.2 (C3), 126.5 (C2), 71.8 (d, *J* = 4.9 Hz, C5), 61.9 (d, *J* = 6.4 Hz, C8/C10), 61.8 (d, *J* = 6.5 Hz, C8/C10), 39.6 (d, *J* = 135.6 Hz, C6), 32.5 (d, *J* = 14.1 Hz, C7), 16.4 (d, *J* = 6.2 Hz, C9/C11), 16.2 (d, *J* = 6.1 Hz, C9/C11).

^{31}P NMR (245 MHz, $CDCl_3$): δ 28.5 (s, 1 P, C6-P).

FTIR (ν_{max}, cm^{-1}): 3386 (br w, OH), 2981 (w), 2932 (w), 2908 (w), 1491 (w), 1443 (w), 1394 (w), 1369 (w), 1218 (m), 1164 (w), 1093 (m), 1049 (s), 1025 (s), 964 (m), 912 (w), 833 (m), 782 (w).

HRMS (ESI): calculated for $C_{13}H_{20}O_4PClNa$ $[M+Na]^+$ 329.0680, found 329.0678.

R_f = 0.36 (35% EtOAc/60% hexane/5% MeOH).

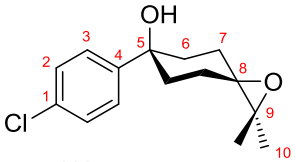


387

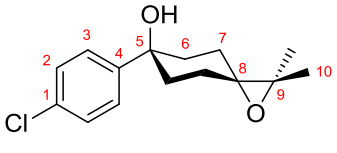
4-(4-Chlorophenyl)-4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide (387): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-

diazaspiro[4.5]dec-1-ene 8,8-dioxide (**325**) (0.234 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% → 40% EtOAc/CH_2Cl_2) provided the title compound as a white crystalline solid (90.8 mg, 0.348 mmol, 70%), m.p. 196-198 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2 H, H2), 7.37 (d, *J* = 8.7 Hz, 2 H, H3), 3.58 (td, *J* = 13.8, 3.5 Hz, 2 H, H7a), 3.00 – 2.91 (m, 2 H, H7b), 2.68 (td, *J* = 14.5, 2.6 Hz, 2 H, H6a), 2.18 – 2.10 (m, 2 H, H6b), 1.78 (br s, 1 H, OH).
^{13}C NMR (150 MHz, $CDCl_3$): δ 144.6 (C4), 134.2 (C1), 129.1 (C3), 125.8 (C2), 70.6 (C5), 47.3 (C7), 37.1 (C6).
FTIR (ν_{max}, cm^{-1}): 3404 (br m, OH), 1595 (w), 1485 (m), 1433 (w), 1393 (m), 1363 (w), 1334 (m), 1284 (s), 1272 (s), 1243 (w), 1224 (w), 1193 (w), 1172 (m), 1119 (s), 1093 (m), 1068 (s), 1023 (m), 1013 (m), 984 (w), 968 (m), 931 (s), 878 (w), 853 (w), 823 (s).
HRMS (ESI): calculated for $C_{11}H_{13}O_3SClNa$ $[M+Na]^+$ 283.0166, found 283.0170.
R_f = 0.34 (20% EtOAc/CH_2Cl_2).



388, *diastereomer A*



388, *diastereomer B*

6-(4-Chlorophenyl)-2,2-dimethyl-1-oxaspiro[2.5]octan-6-ol (388): Following the general procedure for oxidative coupling using 9-methoxy-2,2,9-trimethyl-1,10-dioxa-7,8-diazadispiro[2.2.4^6.2^3]dodec-7-ene (**321**) (0.240 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% EtOAc/hexane) provided the title compound as separable diastereomers (1:1) as a white crystalline solids (A: 55.5 mg, 0.208 mmol; B: 60.3 mg, 0.226 mmol; combined yield 87%), m.p. 168-171 °C for diastereomer A and m.p. 156-159 °C for diastereomer B.

Diastereomer A:
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.6 Hz, 2 H, H2), 7.30 (d, *J* = 8.6 Hz, 2 H, H3), 2.20 (td, *J* = 13.5, 3.6 Hz, 2 H, H7a), 2.12 (td, *J* = 13.5, 3.6 Hz, 2 H, H6a), 1.84 – 1.79 (m, 2 H, H6b), 1.78 (br s, 1 H, OH), 1.55 – 1.49 (m, 2 H, H7b), 1.35 (s, 6 H, H10).
^{13}C NMR (150 MHz, $CDCl_3$): δ 147.5 (C4), 132.8 (C1), 128.5 (C3), 126.2 (C2), 72.5 (C5), 65.1 (C8), 63.3 (C9), 36.4 (C6), 25.8 (C7), 20.7 (C10).

FTIR (ν_{max}, cm^{-1}): 3390 (br m, OH), 2928 (m), 1735 (w), 1489 (w), 1432 (w), 1379 (m), 1313 (w), 1245 (m), 1195 (m), 1133 (w), 1095 (s), 1036 (m), 1011 (m), 988 (m), 961 (m), 903 (w), 889 (w), 849 (s), 833 (m), 817 (s), 756 (w).

HRMS (ESI): calculated for $C_{15}H_{19}O_2ClNa$ $[M+Na]^+$ 289.0966, found 289.0960.

R_f = 0.38 (30% EtOAc/hexane).

Diastereomer B:

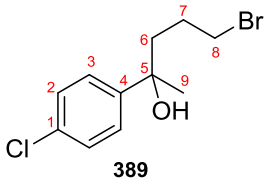
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.6 Hz, 2 H, H2), 7.31 (d, *J* = 8.6 Hz, 2 H, H3), 2.26 – 2.15 (m, 2 H, H7a), 1.98 – 1.88 (m, 5 H, H6 and OH), 1.62 – 1.56 (m, 2 H, H7b), 1.39 (s, 6 H, H10).

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.5 (C4), 133.0 (C1), 128.5 (C3), 126.4 (C2), 72.2 (C5), 66.1 (C8), 62.5 (C9), 38.3 (C6), 26.9 (C7), 20.9 (C10).

FTIR (ν_{max}, cm^{-1}): 3426 (br m, OH), 2938 (m), 1710 (w), 1491 (s), 1474 (m), 1377 (s), 1241 (m), 1174 (w), 1118 (m), 1095 (s), 1064 (s), 1033 (m), 1013 (s), 993 (m), 961 (s), 900 (m), 853 (m), 827 (s).

HRMS (ESI): calculated for $C_{15}H_{19}O_2ClNa$ $[M+Na]^+$ 289.0966, found 289.0967.

R_f = 0.21 (30% EtOAc/hexane).



389

5-Bromo-2-(4-chlorophenyl)pentan-2-ol (389): Following the general procedure for oxidative coupling using 2-(3-bromopropyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**326**) (0.251 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 20% EtOAc/hexane) provided the title compound as a yellow oil (99.0 mg, 0.357 mmol, 87%).

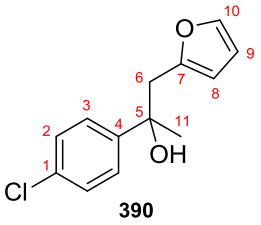
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 2 H, H2), 7.30 (d, *J* = 8.7 Hz, 2 H, H3), 3.39 – 3.29 (m, 2 H, H8), 1.97 – 1.82 (m, 3 H, H6 and H7a), 1.76 (br s, 1 H, OH), 1.72 – 1.63 (m, 1 H, H7b), 1.56 (s, 3 H, H9).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.9 (C4), 132.7 (C1), 128.5 (C3), 126.4 (C2), 74.2 (C5), 42.7 (C6), 34.3 (C8), 30.8 (C9), 27.6 (C7).

FTIR (ν_{max}, cm^{-1}): 3422 (br w, OH), 2967 (w), 1598 (w), 1490 (m), 1453 (w), 1397 (w), 1373 (w), 1293 (w), 1254 (m), 1202 (w), 1163 (w), 1093 (s), 1013 (s), 956 (w), 889 (w), 831 (s), 767 (w).

HRMS (ESI): calculated for $C_{11}H_{14}OBrClNa$ $[M+Na]^+$ 298.9809, found 298.9823.

R_f = 0.34 (20% EtOAc/hexane).



390

2-(4-Chlorophenyl)-1-(furan-2-yl)propan-2-ol (390): Following the general procedure for oxidative coupling using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**322**) (0.210 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% Et_2O/CH_2Cl_2) provided the title compound as an orange gum (90.2 mg, 0.381 mmol, 76%).

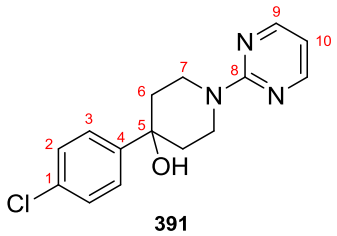
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.6 Hz, 2 H, H2), 7.31 (d, *J* = 1.9 Hz, 1 H, H10), 7.29 (d, *J* = 8.6 Hz, 2 H, H3), 6.26 (dd, *J* = 3.0, 1.9 Hz, 1 H, H9), 5.97 (d, *J* = 3.0 Hz, 1 H, H8), 3.13 (d, *J* = 15.0 Hz, 1 H, H6a), 3.08 (d, *J* = 15.0 Hz, 1 H, H6b), 2.45 (br s, 1 H, OH), 1.54 (s, 3 H, H11).

^{13}C NMR (150 MHz, $CDCl_3$): δ 151.6 (C7), 145.8 (C4), 142.0 (C10), 132.7 (C1), 128.3 (C3), 126.4 (C2), 110.5 (C9), 108.6 (C8), 74.0 (C5), 42.7 (C6), 29.7 (C11).

FTIR (ν_{max}, cm^{-1}): 3429 (br w, OH), 2974 (w), 2910 (w), 1596 (w), 1490 (m), 1455 (w), 1400 (w), 1376 (w), 1266 (w), 1179 (m), 1147 (m), 1090 (s), 1012 (s), 951 (m), 935 (m), 885 (w), 856 (m), 828 (s).

HRMS (ESI): calculated for $C_{13}H_{13}O_2ClNa$ $[M+Na]^+$ 259.0496, found 259.0485.

R_f = 0.21 (10% EtOAc/hexane).



391

4-(4-Chlorophenyl)-1-(pyrimidin-2-yl)piperidin-4-ol (391): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (**323**) (0.263 g, 1.0 mmol) and 4-chlorophenylboronic acid (**329**) (78.2 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 30% Et_2O/CH_2Cl_2) provided the title compound as a colourless gum (83.3 mg, 0.287 mmol, 57%).

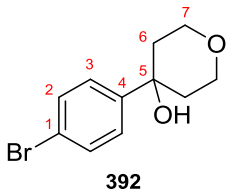
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (d, *J* = 4.8 Hz, 2 H, H9), 7.41 (d, *J* = 8.6 Hz, 2 H, H2), 7.31 (d, *J* = 8.6 Hz, 2 H, H3), 6.47 (t, *J* = 4.8 Hz, 1 H, H10), 4.72 – 4.64 (m, 2 H, H7a), 3.39 (td, *J* = 13.1, 2.6 Hz, 2 H, H7b), 2.07 (br s, 1 H, OH), 2.02 (td, *J* = 13.4, 4.8 Hz, 2 H, H6a), 1.84 – 1.76 (m, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.6 (C8), 157.9 (C9), 146.8 (C4), 133.1 (C1), 128.6 (C3), 126.2 (C2), 109.7 (C10), 71.8 (C5), 40.0 (C7), 38.1 (C6).

FTIR (ν_{max}, cm^{-1}): 3361 (br w, OH), 3027 (w), 2998 (w), 2950 (w), 2920 (w), 2868 (w), 1584 (s), 1546 (s), 1493 (s), 1456 (s), 1392 (m), 1362 (s), 1306 (m), 1272 (m), 1254 (m), 1238 (w), 1215 (m), 1177 (w), 1132 (w), 1091 (m), 1027 (m), 1012 (m), 980 (s), 923 (m), 825 (s), 794 (s).

HRMS (ESI): calculated for $C_{15}H_{17}N_3OCl$ $[M+H]^+$ 290.1055, found 290.1053.

R_f = 0.22 (30% Et_2O/CH_2Cl_2).



392

4-(4-Bromophenyl)tetrahydro-2*H*-pyran-4-ol (392): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-bromophenylboronic acid (100.4 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a white crystalline solid (91.0 mg, 0.354 mmol, 71%), m.p. 114-116 °C. Data are consistent with a reported example.[238]

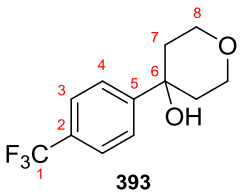
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.7 Hz, 2 H, H2), 7.34 (d, *J* = 8.7 Hz, 2 H, H3), 3.88 (td, *J* = 11.9, 2.0 Hz, 2 H, H7a), 3.85 – 3.79 (m, 2 H, H7b), 2.13 (br s, 1 H, OH), 2.12 – 2.04 (m, 2 H, H6a), 1.65 – 1.58 (m, 2 H, H6b).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.3 (C4), 131.6 (C2), 126.5 (C3), 121.2 (C1), 70.5 (C5), 63.8 (C7), 38.7 (C6).

FTIR (ν_{max}, cm^{-1}): 3399 (br m, OH), 2954 (m), 2869 (m), 1589 (w), 1492 (m), 1388 (m), 1302 (w), 1237 (m), 1221 (w), 1126 (s), 1103 (s), 1073 (m), 1033 (s), 1009 (s), 965 (w), 915 (w), 821 (s), 799 (w).

HRMS (ESI): calculated for $C_{11}H_{13}O_2BrNa$ $[M+Na]^+$ 278.9991, found 278.9994.

***R*$_f$** = 0.22 (40% EtOAc/hexane).



393

4-(4-(Trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-4-ol (393): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-(trifluoromethyl)phenylboronic acid (95.0 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 40% EtOAc/hexane) provided the title compound as a white crystalline solid (85.9 mg, 0.349 mmol, 70%), m.p. 82-84 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 – 7.58 (m, 4 H, H3 and H4), 3.95 – 3.89 (m, 2 H, H8a), 3.89 – 3.83 (m, 2 H, H8b), 2.21 – 2.10 (m, 2 H, H7a), 2.03 (br s, 1 H, OH), 1.69 – 1.60 (m, 2 H, H7b).

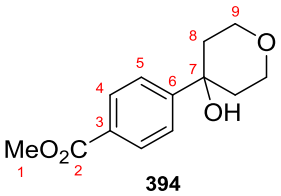
^{13}C NMR (150 MHz, $CDCl_3$): δ 152.1 (q, *J* = 0.9 Hz, C5), 129.5 (q, *J* = 32.4 Hz, C2), 125.5 (q, *J* = 3.7 Hz, C3), 125.1 (C4), 124.2 (q, *J* = 272.0 Hz, C1), 70.8 (C6), 63.8 (C8), 38.7 (C7).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 (s, 3 F, F1).

FTIR (ν_{max}, cm^{-1}): 3402 (br w, OH), 2958 (w), 2873 (w), 1618 (w), 1469 (w), 1409 (w), 1389 (w), 1324 (s), 1303 (m), 1239 (w), 1224 (w), 1164 (m), 1106 (s), 1071 (s), 1034 (m), 1016 (m), 966 (w), 918 (w), 835 (s), 799 (w), 777 (w).

HRMS (ESI): calculated for $C_{12}H_{13}F_3O_2Na$ $[M+Na]^+$ 269.0760, found 269.0752.

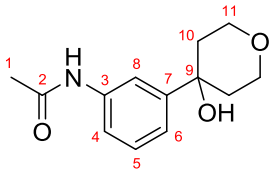
***R*$_f$** = 0.28 (40% EtOAc/hexane).



394

Methyl 4-(4-hydroxytetrahydro-2*H*-pyran-4-yl)benzoate (394): Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 4-methoxycarbonylphenylboronic acid (90.0 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 50% EtOAc/hexane) provided the title compound as a white crystalline solid (36.4 mg, 0.154 mmol, 31%), m.p. 97-98 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.6 Hz, 2 H, H4), 7.54 (d, *J* = 8.6 Hz, 2 H, H5), 3.94 – 3.89 (m, 2 H, H9a), 3.88 (s, 3 H, H1), 3.85 (dd, *J* = 11.3, 5.0 Hz, 2 H, H9b), 2.34 (br s, 1 H, OH), 2.14 (td, *J* = 13.2, 5.0 Hz, 2 H, H8a), 1.64 (d, *J* = 13.2 Hz, 2 H, H8b).
^{13}C NMR (150 MHz, $CDCl_3$): δ 167.0 (C2), 153.3 (C6), 129.9 (C4), 128.9 (C3), 124.7 (C5), 70.8 (C7), 63.8 (C9), 52.3 (C1), 38.6 (C8).
FTIR (ν_{max}, cm^{-1}): 3420 (br w, OH), 2954 (w), 2870 (w), 1722 (s, C=O), 1610 (w), 1575 (w), 1436 (m), 1407 (w), 1387 (w), 1281 (s), 1239 (w), 1224 (w), 1192 (w), 1104 (s), 1035 (w), 1018 (m), 967 (w), 917 (w), 856 (w), 840 (m), 773 (m).
HRMS (ESI): calculated for $C_{13}H_{16}O_4Na$ $[M+Na]^+$ 259.0941, found 259.0945.
***R*$_f$** = 0.30 (50% EtOAc/hexane).



395

***N*-(3-(4-Hydroxytetrahydro-2*H*-pyran-4-yl)phenyl)acetamide (395):** Following the general procedure for oxidative coupling using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (**303**) (0.186 g, 1.0 mmol) and 3-acetamidophenylboronic acid (89.5 mg, 0.5 mmol), purified by silica gel column chromatography (eluent: 10% MeOH/CH_2Cl_2) provided the title compound as a white flaky solid (62.3 mg, 0.265 mmol, 53%), m.p. 128-130 °C.

^{1}H NMR (600 MHz, MeOD-*d*$_4$): δ 7.68 (t, *J* = 1.8 Hz, 1 H, H8), 7.45 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1 H, H4), 7.29 (t, *J* = 7.8 Hz, 1 H, H5), 7.27 – 7.23 (m, 1 H, H6), 3.93 (td, *J* = 11.5, 2.0 Hz, 2 H, H11a), 3.81 (dd, *J* = 11.5, 4.7 Hz, 2 H, H11b), 2.16 – 2.06 (m, 2 H, H10a), 2.12 (s, 3 H, H1), 1.68 – 1.63 (m, 2 H, H10b).

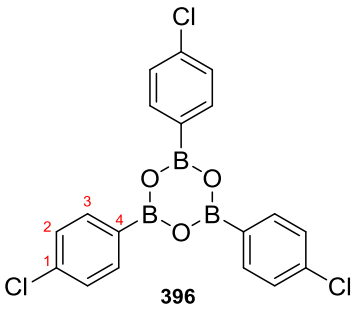
^{13}C NMR (150 MHz, MeOD-*d*$_4$): δ 171.7 (C2), 150.9 (C7), 139.8 (C3), 129.7 (C5), 121.6 (C6), 119.8 (C4), 117.9 (C8), 71.1 (C9), 65.0 (C11), 39.7 (C10), 23.8 (C1).

FTIR (ν_{max}, cm^{-1}): 3388 (br m, OH), 3299 (m, NH), 2957 (m), 2872 (w), 1665 (s, C=O), 1610 (s), 1592 (m), 1553 (s), 1489 (s), 1428 (s), 1372 (m), 1302 (s), 1263 (m), 1239 (m), 1185 (w), 1125 (m), 1095 (s), 1041 (m), 1017 (m), 984 (w), 963 (w), 928 (w), 884 (w), 855 (w), 833 (m), 791 (m).

HRMS (ESI): calculated for $C_{13}H_{17}NO_3Na$ $[M+Na]^+$ 258.1101, found 258.1110.

R_f = 0.33 (10% MeOH/CH_2Cl_2).

5.4.4. Synthetic procedure and characterisation for boroxine **396**



396

2,4,6-Tris(4-chlorophenyl)-1,3,5,2,4,6-trioxatriborinane (396): A suspension of 4-chlorophenylboronic acid (**329**) (0.782 g, 5.0 mmol) in toluene was heated under reflux with equipped Dean-Stark apparatus for 2 h. The reaction mixture was then evaporated under reduced pressure to provide the title compound as a white crystalline solid (0.692 g, 5.0 mmol w.r.t. monomer, 99%), m.p. 286-288 °C (lit. m.p.[239] 284-286 °C). Data are consistent with a reported example.[239]

^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.17 (d, *J* = 8.3 Hz, 2 H, H3), 7.52 (d, *J* = 8.3 Hz, 2 H, H2).
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.3 Hz, 2 H, H3), 7.49 (d, *J* = 8.3 Hz, 2 H, H2).
^{13}C NMR (150 MHz, $CDCl_3$): δ 139.5 (C1), 137.1 (C3), 128.6 (C2). (C4 broadened by quadrupolar relaxation with boron).
FTIR (ν_{max}, cm^{-1}): 1654 (w), 1593 (m), 1563 (w), 1451 (w), 1396 (s), 1363 (s), 1340 (s), 1306 (s), 1256 (m), 1174 (m), 1102 (m), 1085 (s), 1014 (m), 969 (w), 953 (w), 822 (m), 776 (m).

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